β-Adrenergic receptor signaling and modulation of long-term potentiation in the mammalian hippocampus

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Encoding new information in the brain requires changes in synaptic strength. Neuromodulatory transmitters can facilitate synaptic plasticity by modifying the actions and expression of specific signaling cascades, transmitter receptors and their associated signaling complexes, genes, and effector proteins. One critical neuromodulator in the mammalian brain is noradrenaline (NE), which 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, which are known to play important roles in 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 the brain. In this review, we highlight the contributions of noradrenergic signaling in general and β-adrenergic receptors in particular, toward modulating hippocampal LTP. We focus on the roles of NE and β-adrenergic receptors in altering the efficacies of specific signaling molecules such as NMDA and AMPA receptors, protein phosphatases, and translation initiation factors. Also, the roles of β-adrenergic receptors in regulating synaptic “tagging” and “capture” of LTP within synaptic networks of the hippocampus are reviewed. Understanding the molecular and cellular bases of noradrenergic signaling will enrich our grasp of how the brain makes new, enduring memories, and may shed light on credible strategies for improving mental health through treatment of specific disorders linked to perturbed memory processing and dysfunctional noradrenergic synaptic transmission.

Noradrenergic receptor signaling

Norepinephrine (NE), the endogenous ligand for noradrenergic receptors, acts through G-protein-coupled receptors that activate distinct downstream signaling cascades depending on the receptor subtype. These can be broadly classified as α1, α2, β1, and β2-adrenergic receptors (Gelinas and Nguyen 2007). Hippocampal pyramidal cells and dentate gyrus granule cells express all four receptor subtypes (Nicholas et al. 1993; Hillman et al. 2005; Guo and Li 2007). Interneurons also express α1- and β-adrenergic receptors (β-ARs), although there are substantial differences in levels of expression of β1 and β2 receptors in different types of interneurons (Papay et al. 2005; Cox et al. 2008). The α-adrenergic receptors are coupled to Gq or Gi type G proteins and appear to have a role in both memory and synaptic plasticity in some brain regions (for reviews, see Gelinas and Nguyen 2007; Tully and Bolshakov 2010). In contrast, β-ARs signal via activation of Gs type G proteins, followed by stimulation of adenyl 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 and Stork 2000). In addition, β-ARs can also activate ERK through a G protein-independent mechanism mediated by β-arrestin, an adaptor protein that associates with ligand bound β-ARs and recruits ERK and its upstream activators to the receptor (Luttrell et al. 1999; Shukla et al. 2011). PKA and ERK both have critical roles in long-term memory formation and long-term synaptic plasticity in numerous species, including mammals, and they are thought to have a central role in the memory enhancing effects of β-AR activation (Barros et al. 1999; Kandel 2001; Nguyen and Woo 2003; Sweatt 2004).

β-ARs account for the memory-promoting effects of NE

Heightened states of emotional arousal and attention have a powerful effect on memory formation (McGaugh 2013). This is related, in part, to activation of the brain’s noradrenergic system, thereby promoting plasticity in brain regions that mediate enduring behavioral adaptations (Harley 1991; Bouret and Sara 2005). Indeed, acute inhibition of β-ARs with the specific antagonist propranolol significantly impairs the ability of human subjects to remember emotionally charged stories, while having no effect on neutral ones (Cahill et al. 1994; Chamberlain and Robbins 2013). As the amygdala and hippocampus are activated during the acquisition and retrieval of emotional memories, respectively, and as both structures contain β-adrenergic receptors, it is not surprising that propranolol blocked the increased amygdalar and hippocampal activity following the encoding and recall, respectively, of emotional stimuli (Strange and Dolan 2004). Thus, β-ARs are critical for neural processing of emotionally charged memories. Elucidating the detailed mechanisms by which NE promotes memory processing requires the use of animal models which allow for the direct manipulation of the noradrenergic system and the LC. The LC can enhance processing of polymodal sensory input (Bouret and Sara 2005), primarily through its facilitation of synaptic plasticity. The hippocampus is a major processor of polymodal inputs and is densely innervated by noradrenergic fibers from the LC. Behavioral studies indicate that LC stimulation or intrahippocampal NE injection promotes retrieval of spatial and associative memories, and that this requires activation of β-ARs (Devauges and Sara 1991; Przybyszlawski et al. 1999; Sara et al. 1999). Conversely, propranolol inhibits spatial memory (ji et al. 2003b) and long-term, but not short-term, contextual fear memory (ji et al. 2003a) when infused into the hippocampus, further implicating β-ARs in hippocampal memory consolidation (but see Murchison et al. 2004, Debiec and Ledoux 2004; Qi et al. 2008 for evidence that propranolol does not alter performance in contextual fear memory). Furthermore, Izquierdo et al. (1998) found that direct NE injection into rodent CA1 selectively enhanced long-term memory of the inhibitory avoidance task. Interestingly, knockout mice lacking NE (dopamine β-hydroxylase null mutants) display impaired contextual fear memory; however, the memory can be rescued by restoration of NE just prior to memory testing (Murchison et al. 2004). This rescue required activation of hippocampal β-ARs, but not α-ARs (Murchison et al. 2004). Hippocampal infusion of isoproterenol (ISO), a β-AR receptor agonist, also rescued memory in NE-knockout mice (Murchison et al. 2004). Thus, β-AR signaling is critical for contextual memory retrieval in NE-knockout mice.

β-adrenergic receptors facilitate long-lasting hippocampal synaptic plasticity

Norepinephrine 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 (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 hippocampal CA1 region. 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 (Stanton and Sarvey 1984; Frey et al. 1988; Nguyen et al. 1994; Kelleher et al. 2004; Sutton and Schuman 2006; Abraham and Williams 2008). 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; Bourc'houladze et al. 1998; Schafe et al. 1999; Scharf et al. 2002; Costa-Mattioli et al. 2007, 2009). Less robust HFS protocols, such as a single train of 100 Hz stimulation, typically induce a shorter-lasting potentiation of synaptic transmission (lasting ~1–2 h) that does not require translation or transcription. Although noradrenergic receptor activation is not required for the induction of LTP by strong stimulation protocols (Swanson-Park et al. 1999; Murchison et al. 2004), activation of β-ARs potently facilitates the induction of LTP by weaker patterns of synaptic stimulation. For example, β-AR activation enables the induction of protein synthesis-dependent L-LTP by a single 100-Hz train of HFS (Gelinas and Nguyen 2005; Gelinas et al. 2007; Ma et al. 2011). Moreover, 8-pulse stimulation (TPS; 150–900 stimulation pulses delivered at 5–10 Hz), a pattern of synaptic stimulation that alone has little or no lasting effect on synaptic strength, can induce LTP if delivered in the presence of β-AR agonists (Thomas et al. 1996; Katsuki et al. 1997; Moody et al. 1998; Winder et al. 1999; Brown et al. 2000; Gelinas and Nguyen 2005; Havekes et al. 2012; Qian et al. 2012). The induction of LTP by spike-timing-dependent plasticity protocols, where excitatory post synaptic potentials elicited by presynaptic fiber stimulation are paired with postsynaptic action potentials evoked by current injection through an intracellular recording electrode, is also enhanced by β-AR activation (Lin et al. 2003; Seol et al. 2007; Makino et al. 2011).

The overall picture that emerges from studies of β-AR modulation of LTP in the hippocampus is that β-AR lowers the threshold for LTP induction, enabling the induction of LTP by weak patterns of synaptic activity that alone have no lasting effect on synaptic transmission, and facilitating the induction of L-LTP by patterns of synaptic stimulation that induce shorter lasting, protein synthesis-independent LTP. The relative contribution of β1 versus β2-ARs in the enhancement of LTP induction by NE and ISO is unclear, however an early study found that the induction of LTP by TPS in the presence of ISO was impaired in β1-AR but not β2-AR null mutant mice (Winder et al. 1999), indicating a key role for β1-ARs. In contrast, a subsequent study found that the enhancement of TPS-induced LTP by ISO is impaired in both β1-AR and β2-AR knockout mice (Qian et al. 2012). Moreover, the induction of LTP by TPS in the presence of ISO in hippocampal slices from wild-type mice was blocked by the selective β2-AR antagonist ICI-118551 while the 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 due to strain differences in the mice used for these experiments: the knockouts of Winder et al. (1999) were primarily on an FV1 strain background, whereas those used by Qian et al. (2012) were backcrossed to C57BL/6. Moreover, Qian et al. (2012) found that paired-pulse facilitation at Schaeffer collateral fiber synapses in the hippocampal CA1 region is reduced in both β1-AR and β2-AR knockout mice, indicating alterations in presynaptic function. In addition, levels of the postsynaptic adaptor protein Shank are increased in β1-AR mutants while levels of NMDA receptor activators to the receptor (Luttrell et al. 1999; Shukla et al. 2011).


GluN2B subunits are increased in β2-AR mutant mice (Qian et al. 2012). Thus, compensatory and other changes in gene expression associated with null mutations in genes encoding β1 and β2-ARs complicate the interpretation of the plasticity phenotypes in these mutants. Yet another possible contributor to the differential outcomes is quality control of receptor antagonist production by suppliers (Qian et al. 2012). In any event, these studies underscore the sensitivity of noradrenergic receptor studies to genetic and empirical factors that deserve closer scrutiny.

**Molecular mechanisms underlying the enhancement of LTP by β-AR activation**

At the molecular level, β-AR activation has the ability to regulate the signaling events underlying activity-dependent forms of synaptic plasticity in two distinct ways. As discussed in more detail below, this includes direct effects mediated by phosphorylation of ligand- and voltage-gated ion channels involved in the induction and expression of LTP, as well as regulating 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 a protein known as inhibitor-1 (Fig. 1; Brown et al. 2000). When phosphorylated by PKA, inhibitor-1 binds to, and suppresses, protein phosphatase 1, which in turn facilitates activation of protein kinases, such as CaMKII, required for induction of LTP (Blitzer et al. 1998). Down-regulation of protein phosphatase signaling thus provides a second mode of modulation whereby β-AR activation can act in a more global, albeit indirect, way to enhance LTP induction 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 (Thomas et al. 1996; Brown et al. 2000).

**β-adrenergic receptor modulation of NMDA receptor signaling**

In many regions of the brain, including the hippocampus, activation of PKA or β-ARs enhances N-methyl-D-aspartate receptor (NMDAR)-mediated responses (Cerne et al. 1993; Huang et al. 1993; Raman et al. 1996; Blank et al. 1997; Westphal et al. 1999; Bird et al. 2005). Given the central role of NMDAR activation in the induction of LTP, this suggests that modulation of NMDAR function has a pivotal role in the ability of β-AR activation to enhance LTP induction. NMDARs are assembled from four subunits: two obligatory GluN1 subunits and two additional, GluN2A, 2B, 2C, or 2D subunits (Traynelis et al. 2010). In the hippocampus and other forebrain regions, essentially all NMDARs are heteromeric dimers or trimers containing GluN1 subunits and either GluN2A and/or GluN2B subunits (Monyer et al. 1994; Gray et al. 2011). Importantly, all three of these NMDAR subunits are phosphorylated by PKA at sites that regulate NMDAR ion channel function (Fig. 2; Leonard and Hell 1997; Tingley et al. 1997; Murphy et al. 2014). For example, PKA phosphorylation of two sites in the cytoplasmic C-terminal tail of GluN2A subunits (serine 900 and 929) and at serine 1166 in the C-terminus of GluN2B subunits increases channel open probability (Krupp et al. 2002; Maki et al. 2013; Aman et al. 2014). In addition to effects on channel gating, PKA activation also enhances the Ca2+ permeability of NMDAR ion channels (Skeberdis et al. 2006), an effect mediated by phosphorylation of GluN1 subunits at serine 897 and GluN2B subunits at serine 1166 (Aman et al. 2014; Murphy et al. 2014).

Although PKA activation enhances multiple aspects of NMDAR function, it is unclear to what degree direct modulation of NMDARs contributes to the enhancement of LTP by β-AR activation. The induction of LTP by TPS in the presence of ISO is not disrupted in mice expressing truncated GluN2A subunits that lack the entire cytoplasmic C-terminus (Moody et al. 2011). Thus, facilitation of LTP induction by β-AR activation does not require phosphorylation of GluN2A at serine 900 and/or serine 929, suggesting that PKA phosphorylation sites in GluN1 or GluN2B might have a more important role. Consistent with this, β-AR activation increases GluN1 phosphorylation at serine 897 (Murphy et al. 2014) and LTP in the hippocampal CA1 region is strongly reduced in “knock-in” mutant mice expressing GluN1 subunits where serine 897 is replaced with a nonphosphorylatable alanine (Li et al. 2009). However, these mutants also have deficits in basal NMDAR and AMPA receptor-mediated synaptic transmission and the ability of β-AR activation to facilitate LTP induction has not yet been tested. The potential contribution of GluN2B phosphorylation at Ser1166 in the modulation of LTP by β-ARs has also not yet been directly tested. However, β-AR activation induces a robust increase in GluN2B phosphorylation and enhances NMDAR-mediated Ca2+ transients in dendritic spines of hippocampal neurons (Murphy et al. 2014). Thus, PKA-mediated phosphorylation of NMDAR GluN2B subunits may have an especially important role in the modulation of LTP induction by β-ARs.

NMDAR activation is not only dependent on glutamate binding but also requires postsynaptic membrane depolarization to relieve the voltage-dependent Mg2+ ion block of the NMDAR ion channel (Mayer et al. 1984; Nowak et al. 1984). Importantly, β-AR activation has long been known to enhance the excitability of hippocampal CA1 pyramidal cells (for example, see Madison and Nicoll 1982, 1986; Haas and Konnerth 1983; Dunwiddie et al. 1992). Thus, in addition to direct effects on NMDAR ion channel gating and permeability mediated by PKA, β-AR receptor activation could also facilitate NMDAR activation by enhancing membrane depolarization at active synapses (Fig. 2). For example,
AMPA receptors (AMPARs) are generated by the combination of four subunit proteins known as GluA1, GluA2, GluA3, and GluA4 (Traynelis et al. 2010). In the hippocampus, the vast majority (80% or more) of synaptic and extrasynaptic AMPARs are heteromeric receptors containing GluA1 and GluA2 subunits with GluA2/GluA3 subunit-containing receptors accounting for essentially all of the remaining receptors (Wenthold et al. 1996; Lu et al. 2009). Unlike NMDARs, which contain multiple PKA phosphorylation sites, the only site phosphorylated by PKA in GluA1, GluA2, and GluA3 subunits is found at serine 845 in the cytoplasmic C-terminal domain of GluA1 (Traynelis et al. 2010; Lu and Roche 2012). Phosphorylation of this single site, however, regulates multiple aspects of AMPAR function including channel gating (Roche et al. 1996; Banke et al. 2000; Jenkins et al. 2014) and receptor trafficking (Ehlers 2000; Man et al. 2007). Phosphorylation of GluA1 at serine 845 also triggers the insertion of AMPARs into extrasynaptic sites where the receptors appear to be primed for synaptic insertion during LTP induction (Esteban et al. 2003; Oh et al. 2006). Trafficking of AMPARs from this extrasynaptic pool into synapses appears to have a crucial role in LTP (Granger et al. 2013), suggesting that β-AR activation may enhance LTP, at least in part, by increasing the pool of membrane AMPA receptors that are available for synaptic insertion following LTP induction.

Consistent with the notion that AMPARs are an important downstream target of β-AR signaling at synapses, GluA1 subunits are readily phosphorylated at serine 845 following β-AR activation (Vanhoose and Winder 2003; Vanhoose et al. 2006; Tenorio et al. 2010; Moody et al. 2011; Gray et al. 2014). Indeed, through protein interactions mediated by the scaffolding protein PSD-95 and transmembrane AMPAR regulatory proteins (TARPs), GluA1 subunit-containing AMPARs form a complex with β2-adrenergic receptors (Fig. 3; Joiner et al. 2010). This complex also contains PKA and adenylyl cyclase (Joiner et al. 2010), which are recruited into the complex by a kinase anchoring proteins (AKAPs), a family of adaptor proteins that can interact with PSD-95 (Colledge et al. 2000). Thus, β-adrenergic receptors, AMPARs, PKA, and adenylyl cyclase assemble into a large, multicomponent signaling complex that can enable rapid and localized AMPAR phosphorylation following β-AR activation. In cultured hippocampal neurons, peptide inhibitors that disrupt the association of either β2-ARs or AMPARs with PSD-95 block the increase in GluA1 serine 845 phosphorylation induced by β-AR activation (Joiner et al. 2010). Moreover, GluA1 serine 845 phosphorylation induced by β-AR activation in hippocampal neurons is disrupted in mice with a null mutation in the AKAP5 gene, which encodes AKAP79/150 (Zhang et al. 2013). The induction of LTP by TPS in the presence of ISO is also abolished in Akap5 mutants (Zhang et al. 2013) and in hippocampal slices from wild-type mice that are exposed to membrane-permeant peptide inhibitors that disrupt PKA binding to AKAPs (Havekes et al. 2012). Thus, β-AR signaling complexes are crucial for both AMPAR phosphorylation and facilitation of LTP induction. The induction of LTP by TPS in the presence of ISO is also disrupted in Akap12 mutant mice (Havekes et al. 2012). Basal levels of GluA1 serine 845 phosphorylation appear to be normal in these mutants and the deficits in β-AR enhancement of LTP may stem from disruption of ERK signaling downstream of β-AR activation (Havekes et al. 2012). Together, these findings indicate that targeting of PKA and other signaling molecules to β-AR signaling complexes is critical for the enhancement of LTP by β-AR agonists, perhaps by providing a
mechanism that ensures rapid and efficient phosphorylation of AMPAR GluA1 subunits and other signaling molecules following β-AR activation.

Perhaps the strongest evidence implicating AMPAR modulation in the mechanisms underlying β-AR enhancement of LTP comes from experiments using genetically modified mice with knock-in mutations that disrupt specific GluA1 phosphorylation sites. For example, the induction of LTP in the hippocampal CA1 region by TPS in the presence of NE is abolished in mutant mice expressing GluA1 subunits where serine 845 and serine 831 (a site phosphorylated by protein kinase C and CaMKII) have been replaced with nonphosphorylatable alanines (Hu et al. 2007). Strikingly, the ability of systemic epinephrine injections to enhance contextual fear learning is also disrupted in these mutants, suggesting that AMPAR phosphorylation has a key role in the enhancement of memory formation by emotional arousal as well as in β-AR modulation of LTP (Hu et al. 2007). Other experiments have found that the β-AR facilitation of LTP induction at excitatory synapses onto pyramidal cells in visual cortex (Seol et al. 2007) and hippocampal CA1 (Qian et al. 2012) is also abolished in mice expressing GluA1 subunits with a single amino acid substitution that specifically blocks serine 845 phosphorylation. This indicates that serine 845 is required for β-arrenergic modulation of LTP induction. Finally, LTP induction is enhanced and the effects of β-AR activation on LTP are occluded in knock-in mutants where serine 845 (and 831) is replaced with aspartate to mimic phosphorylation (Makino et al. 2011).

Given the broad impact that β-AR activation has on multiple components of the molecular mechanisms underlying LTP, the fact that disruption of a single phosphorylation site in one protein can completely disrupt β-AR enhancement of LTP induction seems surprising. One possibility is that modulation of AMPAR function represents a key point of convergence for all of these signaling pathways. In other words, β-AR activation-induced increases in neuronal excitability and NMDAR activation, as well as modulation of protein kinase and protein phosphatase signaling, all ultimately lead to an enhancement of LTP induction by regulating AMPAR phosphorylation. This AMPAR-centric view has recently been challenged, however, by results indicating that levels of AMPAR GluA1 subunit phosphorylation at serine 845 in the hippocampus are extremely low (Hosokawa et al. 2015). In these experiments, quantitative biochemical approaches were used to measure the stoichiometry of AMPAR subunit phosphorylation at different sites. Remarkably, this analysis revealed that in the hippocampus <0.02% of GluA1 is basally phosphorylated at serine 845. Assuming that synapses contain ~25 GluA1/GluA2 hetero-tetrameric receptors (Nusser et al. 1998; Sheng and Hoogenraad 2007), and thus 50 GluA1 subunits, the low levels of GluA1 phosphorylation at serine 845 found by Hosokawa et al. (2015) indicate that, on average, an AMPAR phosphorylated at S845 is found in only ~1 out of every 100 synapses. Although β-AR activation can induce a two-to-fourfold increase in GluA1 serine 845 phosphorylation (for examples, see Vanhoose and Winder 2003; Vanhoose et al. 2006; Tenorio et al. 2010; Moody et al. 2011; Gray et al. 2014), such low basal levels of phosphorylation suggest that even following β-AR activation only 0.04%–0.08% of all GluA1 subunits will be phosphorylated at serine 845. Importantly, although the vanishingly low levels of basal GluA1 phosphorylation have raised doubts about the role of AMPAR phosphorylation in synaptic plasticity, an earlier study using different approaches found that basal levels of GluA1 serine 845 phosphorylation are much higher (15% or more) (Oh et al. 2006). Clearly, more work is needed to reconcile the disparate findings coming from physiological and biochemical studies of the role of AMPAR phosphorylation in mediating the modulation of LTP induction by β-ARs.

The role of ERK signaling in β-adrenergic receptor modulation of LTP

In addition to the canonical cAMP/PKA pathway, β-AR activation is likely to engage other downstream signaling pathways that contribute to the potent modulatory effects of these receptors on LTP induction. For example, β-AR activation triggers activation of the ERK family of MAP kinases in hippocampal neurons (Roberson et al. 1999; Winder et al. 1999) and pharmacological inhibitors of MEK, the upstream protein kinase responsible for phosphorylating and activating ERK, block the induction of LTP by TPS delivered in the presence of ISO (Winder et al. 1999; Giovannini et al. 2001). Importantly, the ability of TPS protocols to induce LTP is highly dependent on complex spike-like postsynaptic action potential bursting (Thomas et al. 1998). Thus, the ERK-mediated down-regulation of dendritic potassium channels and enhancement of action potential back-propagation in dendrites induced by β-AR activation (Yuan et al. 2002) is likely to have a key role in the enhancement of TPS-induced LTP by β-ARs. Moreover, as discussed below, ERK-mediated changes in protein synthesis are also likely to have a significant role in the β-AR modulation of LTP. A number of important questions remain, however, regarding the role of ERK signaling in mediating the modulatory effects of β-AR activation on LTP induction. For example, although ERK can facilitate cAMP/PKA signaling by phosphorylating and inhibiting some forms of type-4 phosphodiesterases (Hoffmann et al. 1999; Song et al. 2013), the potential contribution of this mechanism to β-AR modulation of LTP has not been tested. In addition, although ERK activation by β-arrestin-dependent β-AR signaling appears to contribute to behavioral learning (Liu et al. 2015), the role of this G-protein-independent form of β-AR signaling in modulating LTP has not yet been investigated.

β-adrenergic receptor modulation of protein synthesis in LTP

Although β-AR activation activates signaling pathways leading to phosphorylation of synaptic proteins known to have key roles in the induction and early phases of LTP maintenance, activation of these receptors also enhances the induction of long-lasting, protein synthesis-dependent LTP by both modest high-frequency synaptic stimulation and TPS (Gelinas and Nguyen 2005; Gelinas et al. 2007; Ma et al. 2011). This indicates that regulation of protein synthesis also contributes to the enhancement of LTP by β-AR activation.

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 the translation of most 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, ERK and mammalian target of rapamycin (mTOR), participate in the formation of the eukaryotic initiation factor 4F (eIF4F) complex (Kelleher et al. 2004; Klann et al. 2004; Gelinas et al. 2007; Tsokas et al. 2007). The eIF4F initiation complex is assembled from the initiation factors eIF4A, 4E, and 4G (Fig. 4). In the basal state, formation of this complex is restrained by the 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 is then able to associate with eIF4G and form the eIF4F initiation complex (Fig. 4). In addition, ERK can phosphorylate and activate the protein kinase Mnk1 (MAPK signal-integrating kinase-1), which in turn phosphorylates eIF4E to further enhance translation. Importantly, several
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Figure 4. 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.

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; Klann et al. 2004). For example, 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 appear to have a crucial role in the enhancement of L-LTP induction by β-AR activation (Fig. 4). The induction of L-LTP by weaker, more modest patterns of HFS delivered in the presence of ISO is blocked by ERK and mTOR inhibitors and is 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 enables activity-dependent increases in 4E-BP phosphorylation, as well as increases in eIF4F complex formation (Gelinas et al. 2007). Interestingly, ISO induces 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.

An intriguing feature of β-AR modulation of LTP is that 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 (see Abraham and Bear 1996; Abraham 2008) 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; Vanhoose and Winder 2003; Tenorio et al. 2010), 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 1 h 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...
delivered 30 min prior to or after HFS in the presence of ISO. Heterosynaptic capture was prevented by blocking β-ARs or by genetic suppression of PKA activation (You et al. 2006), suggesting that PKA plays a role in capturing PRPs at recently stimulated synapses (Young et al. 2006; see also Connor et al. 2011b). Preventing GluA2 endocytosis by applying a peptide inhibitor of endocytosis during TPS at a “weak” pathway extended the time window for heterosynaptic transfer of L-LTP, suggesting that processes governing AMPAR endocytosis may be rate-limiting for capture of L-LTP (Connor et al. 2011b). Inhibiting β-ARs with propranolol, or blocking translation during HFS, also prevented heterosynaptic transfer of L-LTP, likely by preventing PRP synthesis (Connor et al. 2011b). However, shifting application of emetine (a translation inhibitor) to overlap with TPS did not block capture of L-LTP (Connor et al. 2011b), indicating that the critical period of PRP synthesis necessary for enabling subsequent capture of L-LTP occurred during ISO plus HFS treatment. These results are consistent with β-AR activation as helping to trigger PRP synthesis that might bolster synapse-based association of events over time.

Understanding how β-ARs contribute to synaptic tagging and metaplasticity may have clinical relevance in light of data demonstrating altered β-AR-dependent heterosynaptic LTP in a Fragile-X Syndrome (FXS) mouse model (Connor et al. 2011a). Fmr1 knockout mice lack fragile-X mental retardation protein (FMRP), which acts as a repressor of translation at synapses (Lagarbauer et al. 2001). Inducing heterosynaptic LTP in Fmr1 KO mice yielded LTP that was sensitive to inhibition of ERK, but not to inhibition of mTOR (Connor et al. 2011a). The mTOR inhibitor rapamycin failed to block the induction of homosynaptic β-AR-dependent LTP in Fmr1 KO mouse hippocampus, consistent with an overproduction of PRPs in the absence of FMRP. Taken together, these data suggest that targeting β-ARs or their downstream effectors may provide novel therapeutic avenues for treating specific disorders that may be causally linked to altered synaptic plasticity.

β-adrenergic receptors are a potential therapeutic target for treating memory disorders

Alterations in noradrenergic neurotransmission may contribute to a number of disorders including Alzheimer’s disease, post-traumatic stress disorder (PTSD), attention deficit disorder, and depression (Berridge and Waterhouse 2003). For example, degeneration of noradrenergic neurons in the locus coeruleus occurs early in Alzheimer’s disease (AD) (Bendayan et al. 2004; Gundersen et al. 2007; Takahashi et al. 2015) and soluble oligomers of amyloid beta (Aβ) proteins can induce a rapid down-regulation and internalization of β2-ARs (Wang et al. 2011; Li et al. 2013). In addition, activation of β2-ARs has been shown to prevent the inhibition of LTP by soluble Aβ at excitatory synapses in both dentate gyrus (Wang et al. 2009) and the hippocampal CA1 region (Li et al. 2013). Activation of β2-ARs may also have a key role in the ability of environmental enrichment to reduce the effects of Aβ peptides on synaptic plasticity (Li et al. 2013). Thus, enhancing noradrenergic receptor signaling may represent a useful approach for treatment of early cognitive impairment in AD (Chalermpranupap et al. 2013).

Alterations in noradrenergic transmission have also been implicated in the underlying pathology of post-traumatic stress disorder (PTSD), with chronic PTSD patients exhibiting elevated levels of urinary and plasma norepinephrine levels and exacerbated noradrenergic responses to psychological stressors (McFall et al. 1990; Yehuda et al. 1992; Strawhun and Geraci 2008). PTSD is characterized by hyper-arousal, avoidance behavior, and recurrence of intrusive memories (Steckler and Rischbrough 2012), though precisely how norepinephrine contributes to symptomology in PTSD remains unclear. Blocking β-ARs with propranolol inhibits the enhancement of memory formation by emotionally charged stimuli in healthy human subjects (Cahill et al. 1994; Londergan et al. 2013), suggesting that excessive noradrenergic receptor activation during traumatic experiences might contribute to the development of PTSD. Moreover, memories are actively updated during recollection and may recapitulate the cellular and molecular processes of de novo memory formation before being stored again, in a process known as “reconsolidation” (Nader et al. 2000). β-AR activation can facilitate reconsolidation of fear memories, suggesting that heightened levels of noradrenergic receptor activation could also lead to facilitated reconsolidation of traumatic memories (Debiec et al. 2011). Importantly, during reconsolidation, memories become labile and can be disrupted by a number of different pharmacological manipulations (Tronson and Taylor 2007), including inhibition of β-ARs (Przybyslawski et al. 1999; Debiec and Ledoux 2004; Debiec et al. 2011). This suggests that blocking β-ARs during memory reconsolidation might offer a potentially beneficial treatment for PTSD. Indeed, propranolol inhibits reconsolidation in healthy human subjects (Kindt et al. 2009; Schwabe et al. 2012) and post-trauma treatments with propranolol can significantly reduce symptoms in patients suffering from PTSD (Vaiva et al. 2003; Brunet et al. 2011). Other studies, however, found little, if any, therapeutic benefit of propranolol treatment in trauma patients (Stein et al. 2007; McGhee et al. 2009; Hoge et al. 2012). There are numerous differences between these studies that could account for these conflicting results including dose, time to first treatment, duration of treatment, method of recall inducement, and the level of trauma experienced by patients. Moreover, work in animal models suggests that the ability of propranolol to inhibit memory reconsolidation may be limited to specific types of memory (e.g., Muravieva and Alberini 2010). Thus, more research is required to validate the broad applicability of β-AR blockers as a treatment for PTSD.

Concluding remarks: a buffet of possibilities

We have given a selective overview of the cellular and molecular mechanisms by which the noradrenergic neuromodulatory system regulates synaptic plasticity in the hippocampus. Clearly, multiple targets for NE’s actions exist. These include cell surface NMDARs and AMPARs, 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, 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 toward basal versus HFS-evoked levels of AMPAR phosphorylation? Do these levels reflect a dynamic interplay between protein kinases and phosphatases anchored at AMPARs? Which particular mRNAs show increased translation rates following activation of β-ARs during L-LTP? This is an important question, as it ultimately will address the issue of which proteins are synthesized de novo and subsequently incorporated into existing networks of effector proteins. Can β-ARs in hippocampal neurons signal to the nucleus to trigger transcriptional changes and/or epigenetic modifications that contribute to L-LTP? It will also be important to use computational, systems, and behavioral approaches, to address the noradrenergic system’s roles in gating behavioral and neuronal network adaptations.
A prime directive of the noradrenergic system is to reorganize neural network activity in a way that enables rapid behavioral adaptation in the face of environmental challenges. Although our review has not covered systems neurophysiology and behavioral neuroscience in depth, it is clear that the endpoint of all of the molecular and cellular machineries discussed here is the generation of productive behavioral actions. A major challenge for researchers is to elucidate how β-ARs cooperate with other neuromodulatory receptors to fine-tune goal-directed behaviors in an intact organism. Research on synaptic tagging and capture of plasticity-related proteins at the cellular level has advanced to the stage where we can now seek out exact behavioral “equivalents,” and consequences, of tagging and capture. Genetic block or enhancement of expression of specific “tags” (e.g., β-ARs, AKAPs, CaMKII, or AMPAR subunits such as GluA1), or block of capture of proteins, in definable neural networks can be used to gauge the behavioral consequences of such manipulations. Also, the translational potential (“bench to bedside”) of β-AR blockers, functional modifiers of AKAPs, or AMPAR agonists, as treatments for PTSD and dementia-associated memory loss, needs to be explored at the interface between systems neurophysiology and behavioral neuroscience. It may turn out that multiple strategies, enveloping pharmacological, and behavioral therapies, will be optimal for treating these very complex disorders. Given the ubiquitous influences of the noradrenergic system on a broad range of brain functions such as arousal, perception, attention, learning, and memory, we have no doubts about the challenges, but also the important opportunities, that lie ahead of us.

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