Noradrenergic Regulation of Hippocampus-Dependent Memory

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Abstract: Neuromodulation regulates critical functions of CNS synapses, ranging from neural circuit development to high-order cognitive processes, including learning and memory. This broad scope of action is generally mediated through alterations of the strength of synaptic transmission (i.e. synaptic plasticity). Changes in synaptic strength are widely considered to be a cellular representation of learned information. Noradrenaline is a neuromodulator that is secreted throughout the brain in response to novelty or increased arousal. Once released, noradrenaline activates metabotropic receptors, initiating intracellular signaling cascades that promote enduring changes in synaptic strength and facilitate memory storage. Here, we provide an overview of noradrenergic modulation of synaptic plasticity and memory formation within mammalian neural circuits, which has broad applicability within the neurotherapeutics community. Advances in our understanding of noradrenaline in the context of these processes may provide a foundation for refining treatment strategies for multiple brain diseases, ranging from post-traumatic stress disorder to Alzheimer’s Disease.

Keywords: Noradrenaline, memory, hippocampus, beta-adrenergic receptors, long-term potentiation, synaptic plasticity.

1. INTRODUCTION

All high-order cognitive functions are influenced to some degree by neuromodulatory signaling. Projections from brain stem nuclei innervate multiple regions of the Central Nervous System (CNS) to deliver a broad range of neuromodulatory transmitters. Although much remains to be elucidated, significant strides have been made in our understanding of the neuronal and molecular implications of activating neuromodulatory receptors, including characterization of their effects on the encoding and storage of information within neural circuits.

Modifications of synapses serve as well-established cellular analogs of information storage. This “synaptic plasticity” [1] exists in multiple forms, the properties of which can be altered by neuromodulators. One of the most fruitful brain regions for studying this synaptic plasticity is the hippocampus, a brain region required for forming spatial and contextual memories [2]. The hippocampus consists of a trisynaptic loop with multiple subregions that are densely innervated by neuromodulatory inputs, thereby making this neural circuit an excellent model system for studying how activation of synaptic neuromodulatory receptors may alter information processing. Emotional or arousing experiences induce the secretion of noradrenaline (NA), a neuromodulator that influences cell excitability, synaptic physiology, and memory processing. Neurons within the locus coeruleus, the primary source of NA in the brain, fire more frequently in response to detection of novel or arousing stimuli, thereby inducing NA release throughout the neural axis [3]. Once released, NA binds to metabotropic receptors, initiating a cascade of intracellular signals that can induce long-term changes in the efficacy of synaptic transmission [4, 5]. In this review, we discuss the effects of NA on memory processes in the mammalian brain, focusing particularly on the link with beta-Adrenergic Receptors (β-ARs), which are strongly implicated in the memory-promoting effects of NA. A broad understanding of how neural circuits supporting cognitive function are modified by noradrenaline is important for those interested in developing novel therapeutics for use in the treatment of neurological disorders.

2. NEUROMODULATION: THE BASICS

Canonical synaptic transmission consists of a transient, local signal that mediates ongoing synaptic “chatter” between brain cells. This fast-synaptic transmission is either excitatory (promotes cell firing) or inhibitory (depresses cell excitability/firing) and is usually restricted to ligand-gated channels at activated synapses. In contrast, neuromodulators trigger longer lasting changes in neuronal responses that can be cell-wide in their effects. This “neuromodulation” is mediated through activation of intracellular second messenger.
cascades that can influence processes encompassing the entire cell, with signal half-lives far exceeding localized synaptic transmission [6]. These properties contribute to pleiotropic effects of neuromodulators, ranging from rapid changes in cell excitability to shaping synaptic strength, up to and including epigenetic regulation of transcription [7]. This broad spectrum of functional outcomes provides a basis for the established roles of neuromodulators in higher-order cognitive processes as well as in the mechanistic failings that underlie human brain disease.

The primary source of NA in the CNS is the Locus Coeruleus (LC), a brainstem nucleus located in the caudal pons. The LC projects diffusely throughout the brain, including cortical (cerebral cortex) and subcortical (amygdala, cerebellum, hippocampus and thalamus) structures [3, 8]. Noradrenergic receptors are G-protein (guanine nucleotide-binding regulatory proteins) coupled, meaning that activation of these receptors initiates a cascade of signaling dependent upon the particular G-protein that they couple to. The physiological effects of NA depend on the receptor subtype that NA binds to. These receptors fall into 2 broad categories (α or β) that can be further subdivided based on their respective structures (α1, α2 and β1, β2, β3). Depending upon the relative expression levels, subcellular localization and rates of desensitization, NA receptors can affect a wide array of neuronal properties including cellular excitability, synaptic transmission and plasticity, protein synthesis and epigenetic modifications.

The convergence of these various cellular processes contributes to bidirectional changes in synaptic strength, particularly during periods of increased cell activity. When synaptic stimulation is induced in the presence of NA, long-lasting increases in the physiological strength of synapses, a process known as Long-Term Potentiation (LTP) [9], can be induced. LTP is an activity-dependent increase in synaptic strength widely considered to be a cellular model for learning and memory due to its associative, and enduring, properties [10, 11]. Most glutamatergic (excitatory) synapses in the brain have the capacity for LTP, and LTP-like processes have been observed in vivo during ongoing learning [12]. Conversely, synaptic weakening can also be induced when cells undergo prolonged, low-frequency stimulation, a process known as Long-Term Depression (LTD) [13, 14]. The direction (potentiation or depression) and magnitude (relative strength) of synaptic change is subject in part to the noradrenergic receptor subtype that is engaged in the presence of NA. Here, we will focus on the effects of adrenergic receptors in the hippocampus given its prominent role in various aspects of memory processing [15]. Pharmacological tools with high receptor specificity have been used to demonstrate the unique signaling cascades downstream of the different receptors and the relative contribution of adrenergic receptors to various forms of synaptic plasticity.

3. NORADRENERGIC MODULATION OF SYNAPTIC PLASTICITY: ALPHA-ADRENERGIC RECEPTORS

The roles of α1-adrenergic receptors in synaptic plasticity vary depending on the hippocampal subregion being investigated. Activation of α1-adrenergic receptors has a modest effect on the induction and maintenance of LTP when paired with weak electrical stimulation in area CA1 [16, 17]. With-
crease excitatory transmitter release and enhance the initial expression of LTP.

Unlike the dentate gyrus and CA3, β-ARs in area CA1 are not required for the induction of LTP by HFS, consistent with a modulatory role for β-AR signalling in this subregion [37-40]. Consistent with this, long trains of Low-Frequency Stimulation (LFS), that normally induce a transient depression of synaptic strength through recruitment of protein phosphatases [19, 41, 42], can be converted to a potentiating stimulus when applied in the presence of β-ARs. Pairing β-AR activation with a normally synapse-depressing LFS permits induction of LTP [41, 43, 44]. This form of LTP is dependent on the PKA and Extracellular-signal Regulated Kinase (ERK) signaling cascades [41, 44, 45]. β-AR activation during LFS increases the amplitude of “complex spikes”, bursts of action potentials that facilitate the generation of LTP. This effect on complex spiking is evident during theta frequency stimulation, which mimics endogenous brain rhythms generated during spatial exploration [40, 46]. Within the CA1, there may be regionally selective effects along the dorsal-ventral axis in response to experiences that modulate NE release. Exposure to stress early in development amplified the facilitating effects of isoproterenol on LTP within the ventral hippocampus whereas the reverse was observed in the dorsal hippocampus [47]. Expression of β1-ARs was upregulated exclusively in the ventral hippocampus, suggesting that juvenile stress alters LTP properties in a region-specific manner by increasing sensitivity to NE.

LTP can be differentiated into different phases that are mechanistically distinct. Following the induction phase, which requires NMDA receptor activation [48], a maintenance phase of LTP emerges that is mediated by increased retention of AMPA receptors at synapses [11, 49]. Pairing β-AR stimulation with tetanisation that is normally sub-threshold for long-lasting LTP generates persistent LTP that requires protein synthesis and ERK signaling [43, 50]. Additionally, β-adrenergic signaling recruits the kinase, mammalian target of rapamycin (mTOR), to promote increased stability of LTP in this subregion [50]. Activation of β-ARs appears to serve as a permissive gate, allowing for the induction of enduring forms of LTP by subthreshold stimulation protocols [43]. The effects of ISO were mimicked through selective stimulation of β2-, but not β1-ARs [51]. Activation of β2-ARs enhanced theta-LTP through phosphorylation of serine 845 (s845) on GluA1-containing AMPARs. Contrasting with previous findings implicating only the β1-AR [44], the potentiating effects of ISO on theta LTP was impaired in both β1- and β2-AR knockout acute slices. However, this may have been the result of compromised presynaptic function or developmental shifts in synaptic protein complement or signaling mechanisms in the respective knockouts.

Beyond direct effects on cell excitability and synaptic plasticity, NA can initiate “metaplastic” effects that alter the basal state of synapses such that they are primed for future long-term plasticity [52]. Application of ISO can recruit “silent” metaplastic processes that don’t observably change the basal strength of synapses but can still permit subsequent induction of late-LTP [53]. This “silent” metaplasticity of LTP recruits translation downstream of ERK and mTOR pathways. Furthermore, this metaplasticity appears to expand the temporal window for associative induction of LTP through a protein synthesis-dependent process [53, 54]. These findings suggest that NA, acting through β-ARs, may increase the temporal window for associating disparate synaptic events.

How neural circuits associate events at the cellular level, particularly when these events are separated in time, is an open question. Pioneering research from Julietta Frey and her colleagues found that strong activation of synapses can generate plasticity-related proteins that are utilized by weakly activated synapses converging on the same neurons [55]. Can β-ARs engage similar processes to promote heterosynaptic transfer of LTP? This idea was tested using a heterosynaptic stimulation protocol in which homosynaptic β-AR LTP was induced in one synaptic pathway while a second pathway received weak theta-frequency stimulation after a 30 minute delay. Normally, this theta-frequency stimulation induces a low amplitude, rapidly decaying form of LTP. However, induction of β-AR LTP at the first synaptic pathway transferred the weak heterosynaptic LTP into enduring potentiation. Inhibiting translation during homosynaptic, but not heterosynaptic, LTP induction reduced the maintenance of LTP at both pathways [56]. Activation of β-ARs using ISO generates these Plasticity-Related Proteins (PRPs) that can then be “captured” at neighboring synapses to bolster LTP in a heterosynaptic manner [56]. The capture of these PRPs relied on PKA and was insensitive to translation inhibition, consistent with PRPs being generated by prior activation of β-ARs [56]. Interestingly, blocking GluA2 endocytosis extended the temporal window for heterosynaptic transfer of LTP from 30 minutes to 1 hour [56]. Collectively, these results demonstrate that β-AR stimulation is capable of expanding the time window through which synaptic events associated with ongoing cellular activity can be molecularly linked, likely through utilization of translation-dependent processes that converge on GluA2-containing AMPARs. The mechanisms required for synapse-specific recruitment of molecules required for heterosynaptic transfer have not yet been fully identified.

NA can also cooperate with other neuromodulatory transmitters to synergistically enhance LTP. Previous research found that the amplitude and duration of LTP within the Schaeffer collateral-CA1 pathway could be enhanced through co-application of ISO and carbachol, a muscarinic receptor agonist [57]. It was later demonstrated that this synergistic effect depends on β1-ARs and M1 muscarinic receptors acting through ERK and mTOR signaling cascades to recruit protein synthesis machinery necessary for boosting LTP [58]. Conversely, co-activation of α1 and muscarinic receptors within this circuit induced LTD [59]. This suggests that NA acting in concert with other neuromodulators can induce bidirectional changes in synaptic strength in the hippocampus. Further studies are needed to determine if these interactive properties are utilized by other brain regions to increase synaptic modifiability or enhance memory processing.
Given the prominent physiological effects of noradrenergic neuromodulation throughout the CNS, a key role for the noradrenergic system appears to be the enhancement of neural network modifiability in response to contexts that require cognitive and behavioural shifts [60]. Several of the brain structures innervated by noradrenergic inputs, including the prefrontal cortex [61, 62] and hippocampus [2, 15, 63, 64], are involved in memory processing. This suggests that NA may promote the acquisition and retention of information at a cellular level, most likely by promoting alterations in synaptic strength. Here, we highlight findings that demonstrate the effects of NA on the hippocampal memory system, underscoring the mechanisms that may contribute to these effects.

5. DOWNSTREAM EFFECTORS OF NORADRENA-LINE

Progress had also been made in characterizing the molecular mechanisms through which β-ARs regulate glutamatergic synapse plasticity. β2-ARs have been observed in multi-protein complexes containing GluA1 [65], L-type calcium channels [66] and A-kinase anchoring protein 5 (AKAP5; known as AKAP150 in mice) [67], which serves as a molecular scaffold that brings β-ARs into close physical proximity to its downstream effectors, including PKA and AMPA receptors. Stimulation of β-ARs normally increases the phosphorylation of GluA1 on Ser-845, which was dramatically reduced in the hippocampi of AKAP5 knockout mice [67]. Prolonged theta LTP was also diminished in AKAP5 knockouts, consistent with a loss of PKA anchoring which otherwise promotes GluA1 phosphorylation and GluA1 synaptic insertion, key mechanisms supporting this form of β-AR-dependent LTP. An additional anchoring protein that coordinates β2-AR interactions with its effectors is gravin. Mice lacking the gravin-α isoform exhibited deficits in both theta burst LTP and LTP induced by pairing LFS with ISO, which both require β2-AR activation [51, 68]. A PKA-independent form of LTP (massed 4-train LTP) was intact in gravin-α mutants, and pharmacological inhibition of PKA anchoring in wild-type mice impaired LFS+ISO LTP maintenance indicating that compromised PKA signaling or defective localization downstream of β2-AR activation likely contributes to the plasticity deficits. It is noteworthy that phosphorylation of β2-ARs switches its coupling from Gα to Gai, thereby promoting activation of ERK1/2. Both β2-ARs and learning-induced ERK1/2 phosphorylation were reduced following loss of gravin-α, which contributed to impaired object-place recognition memory [68]. These data suggest that signaling complexes coordinated by gravin critically regulate β2-AR-mediated synaptic plasticity in hippocampus, in part through maintaining localization of PKA.

In addition to immediate effects on the induction of homosynaptic LTP [43, 50, 69], stimulating β-ARs can initiate a long-term “silent” form of plasticity in which synapses are primed for the future induction of plasticity [53]. This “metaplasticity” appears to promote future plasticity through activation of signaling cascades that couple to protein synthesis, although whether the endogenous signal (NA) could similarly induce metaplastic effects, and the identity of the upregulated translation products, remained unclear. Further experiments have revealed specific proteins that are upregulated during β-AR metaplasticity. Consistent with results using ISO, application of NA facilitated the induction of LTP when tetanisation was applied 30 min later [70]. Metaplasticity induced by NA was prevented by blocking either β-ARs, translation or transcription during the NA treatment period. Puromycin incorporation confirmed an upregulation of translation following NA treatment in the hippocampal CA1 region. Polysomal profiling identified GluA1 and GluA2 AMPA receptor subunits as translation products that were specifically upregulated during NA metaplasticity [70]. Together with previous findings linking β-AR activation to increased surface expression of GluA1 [53], these data reveal a model in which NA, acting through β-ARs, promotes both the synthesis of new AMPA receptor subunits and their insertion and retention at synapses. The selective upregulation of plasticity-related proteins (GluA1 and GluA2) provides supporting evidence against the contention that inhibition of translation has global, non-specific effects on protein synthesis rates that would indirectly impede potentiation. Further research is required to determine if translation rates for other proteins implicated in synaptic plasticity are upregulated and to further identify mechanisms that promote the selective synthesis of GluA1/GluA2 during noradrenergic metaplasticity of LTP.

Dual synaptic pathway recordings suggest that activation of β-ARs can facilitate both homosynaptic and heterosynaptic LTP. Specifically, pairing ISO with “strong” tetanisation at one pathway can allow subthreshold “weak” stimulation of second synaptic pathway to induce long-lasting LTP [56]. Initial mechanistic characterization suggested that this heterosynaptic plasticity was mediated through upregulation of translation, resulting from recruitment of ERK and mTOR downstream of β-ARs. ERK and mTOR. One possible mechanism for coupling β-ARs to ERK activity is through exchange protein activated by cyclic-AMP (Epac) signaling, which is required for homosynaptic β-AR LTP [71]. Stimulation using NA similarly enhanced heterosynaptic LTP [72]. Interestingly although PKA was required for expression of heterosynaptic LTP, inhibition of Epac, which links cAMP to ERK signalling, impaired both homosynaptic and heterosynaptic LTP. This is in accordance with spatial mechanistic modelling that suggests PKA mediates dendritic spine-restricted signalling, whereas Epac modulates dendritically-localized processes required for LTP expression [73]. Alternatively, Epac may perform multiple roles in heterosynaptic plasticity, contributing to stabilization of LTP and perhaps also generation of plasticity proteins and setting of synaptic tags required for LTP capture. Going forward, it will be important to identify the translation products and molecular events that serve as activity-induced tags during β-AR-dependent heterosynaptic LTP, and to determine how PKA and Epac may act in tandem to coordinate molecular processes required for heterosynaptic capture of LTP.

The influence of β-ARs extends beyond the synapse to modulation of the nucleosome. Similar to ISO, the endogenous transmitter NA paired with HFS induces a long-lasting,
protein synthesis-dependent form of LTP [7]. Given that NA promotes activation of ERK, a molecule capable of translocating to the cell nucleus to influence synaptic consolidation and memory formation, Maity and others [7] tested whether transcriptional mechanisms are engaged during NA-LTP. Inhibition of transcription prevented the expression of NA-LTP. NA appears to regulate transcription by enhancing DNA methyl transferase activity, recruiting histone acetyl-transferase CBP/p300 and inhibiting histone deacetylases [7]. Histone phosphorylation was also implicated in NA-LTP, as inhibition of Aurora kinase-B (which phosphorylates histones) impaired NA-LTP, whereas levels of phosphorylated histone H3 were increased following induction of NA-LTP [7]. Noradrenergic enhancement of heterosynaptic plasticity similarly required transcriptional regulation, specifically histone acetylation and DNA methylation [74]. Collectively, these results add transcriptional regulation at the level of the epigenome to the core menu of mechanisms supporting long-term modification of synapses by β-ARs.

6. NORADRENALINE AND MEMORY FORMATION: ALPHA-ADRENERGIC RECEPTORS

Foundational studies demonstrating the requirement for the hippocampus in declarative and spatial memories extend back more than 50 years [63], and have been validated in rodent [75] and non-human primate models [76]. Spatial “maps” of environments are formed within the hippocampus circuit [77], and this process is subject to modulation by NA. The capacity for updating of spatial maps appears to be regulated by LC activation, whereas pharmacological silencing of the LC prevents forming new maps in novel environments [78]. NA enhances memory for a variety of hippocampal tasks and has been linked to neuropsychiatric disorders characterized by excessive memory formation or recall, including Post-Traumatic Stress Disorder (PTSD) [79]. Below we outline the relative contributions of the various adrenergic receptor subtypes to memory processing.

Consistent with their limited roles in synaptic plasticity, α-ARs make modest, but detectable, contributions to hippocampal memory processing [80, 81]. Acquisition of a spatial memory was improved when rats were given an α-AR agonist prior to a spatial water maze task training [82, 83]. However, increased expression of α-ARs has been associated with impaired performance on spatial memory tasks, likely due to an inhibitory effect on presynaptic transmission.

7. NORADRENALINE AND MEMORY FORMATION: BETA-ADRENERGIC RECEPTORS

β-ARs are chiefly responsible for noradrenergic effects that predominantly promote memory formation. Administration of a β-AR antagonist blocks the formation of a memory in both contextual fear conditioning and the Morris Water Maze, two tasks dependent upon CA1 function for robust performance [84, 85]. Inhibition of β-ARs in the dorsal hippocampus similarly impairs novel object recognition memory whereas pharmacological stimulation of β-ARs increases the persistence of this type of memory [86].

Memory can be subdivided into phases with distinct physiological, molecular and temporal characteristics. β-ARs appear to preferentially regulate long-term (LTM), rather than short-term (STM), memory processes. Injection of NA into area CA1 of the hippocampus selectively enhances LTM without altering STM [87, 88]. Blocking these receptors after training similarly impairs LTM for contextual fear conditioning, suggesting an extended requirement for these receptors beyond initial encoding [85]. Consistent with a role in LTM, injection of β-AR antagonists inhibits LTM for an associative task when applied two hours after training [89]. Based on β-AR antagonism preferentially effecting late phases of memory, it appears that the noradrenergic system mediates memory consolidation, the process through which memories become stabilized [90, 91], although conflicting results have been reported [92].

Memory can also be defined based on processing phases, with acquisition, consolidation, and retrieval stages discernable across memory tasks despite considerable temporal variability. Across these tasks, these stages selectively recruit specific brain regions and molecular mechanisms, allowing researchers to better isolate different memory processes [93]. For example, pairing weak foot shocks with infusion of isoproterenol into the lateral amygdala facilitated learning (acquisition) of an aversive association memory which required recruitment of calcium-permeable AMPA receptors [94]. The consolidation phase of this same memory required delayed onset ERK activation, suggesting β-ARs recruit divergent signaling cascades to facilitate unique phases of memory, thereby enhancing both initial learning and subsequent storage (consolidation) of new information. Evidence suggests that NA mediates memory retrieval in the hippocampus through activation of β-ARs [37, 95, 96]. Stimulation of the LC or injection of NA into the hippocampus promotes retrieval of memory for food-motivated maze and inhibitory avoidance tasks [95, 96]. To further confirm a role for NA in retrieval, researchers have probed mice that genetically lack endogenous NA and adrenaline (Dbh-/-). These mice displayed impaired spatial memory consolidation [92]. Although Dbh-/- mice learned the location of an escape platform in the Morris Water Maze at rates comparable to controls, they showed decrease preference for the correct platform quadrant in subsequent probe trials [92]. This suggests that NA is not required for memory formation but is required for memory consolidation.

Beyond initial memory consolidation, β-ARs are also implicated in the process of updating and re-stabilizing previously stored memories, known as reconsolidation. Blockade of β-ARs after the reactivation of a memory induces amnesia when this memory is tested at a later time point, consistent with disruption of reconsolidation [97]. β-AR signaling was also required for the extinction of memory, a process which allows new associations to be made about previously-experienced stimuli. Overall, β-ARs may contribute to updating memories by regulating the reconfiguration of recalled memories. The mechanisms remain to be elucidated.

Considerable evidence suggests that enduring forms of plasticity represent a cellular mechanism for memory storage...
in the brain [98-100]. Given the established roles for NA in modulating both synaptic plasticity and hippocampus-dependent behaviors that engage memory processing, there may be a correlation between the synaptic and mnemonic effects of NA on behavior. Exposure to novel stimuli is often considered to be an arousing experience, and it can enhance both population spike amplitude (a measure of cell excitability) and reinforce LTP within the dentate gyrus [101, 102]. These effects result from spike bursting in LC neurons driving NA secretion within the dentate gyrus and they can be partially blocked by a β-AR antagonist. This suggests that novel stimuli recruit the noradrenergic system to increase information transmission and storage in the hippocampus, creating a behavioural “gate” for information storage and consolidation.

Mechanistic parallels between enduring synaptic plasticity and LTM further suggest that NA is capable of facilitating hippocampus-dependent memory. Activation of β-ARs enhances LTP induction and maintenance in a frequency-dependent manner in CA3, CA1 and the subiculum [36, 43]. LTP stability is associated with recruitment of protein synthesis, likely including the increased translation of GluA1, an AMPA receptor subunit associated with learning and memory [70]. Importantly, upregulation of translation is required for both LTP and LTM [31]. NA might provide a saliency signal that engages translation to enhance the potency of stimuli that are subthreshold for making new long-term associative memories.

8. IN VIVO EVIDENCE FOR β-ARS AS MEMORY MEDIATORS

Evidence for direct effects of NA acting through β-ARs in vivo continues to accumulate. The LC activates in response to novel experiences, which promote secretion of NA throughout the brain, including all subregions of the hippocampus. In freely behaving adult rats, pairing baseline electrical stimulation of the Schaeffer collateral pathway with stimulation of the LC induced LTD, which was prevented by blocking β-AR activation [103]. Spatial memory was likewise enhanced by pairing LC activation with Schaeffer collateral pathway stimulation and it was similarly blocked by antagonism of β-ARS. Generally, learning can enhance synaptic depression or potentiation throughout the hippocampal circuit in vivo, and this “learning-facilitated plasticity” is contingent upon neuromodulation. Exploration of an empty holeboard, constituting a form of spatial learning, converts decaying LTD into enduring, stable LTP at mossy fiber-CA3 synapses [104]. Similarly, exploration of spatial “landmarks” in a novel environment converts transient LTD into a persistent LTD, an effect that similarly required β-AR activation. Collectively, these results suggest that detection of novelty drives locus coeruleus activity and NA secretion, which lower the thresholds for bidirectional changes in plasticity to optimize the processing capacity of hippocampal circuits.

CONCLUSION

Collectively, these findings demonstrate that NA is a powerful contributor to various aspects of memory processing, effects likely mediated by increasing the lability of CNS synapses. Going forward, it will be important to determine the relative contributions of NA signaling in additional neural circuits associated with higher-order cognitive functions. Additionally, the synergistic mechanisms between NA and other neuromodulatory substances remains largely unexplored. For example, important questions still remain about NA signaling in the context of sleep-dependent memory consolidation. Combination of in vivo imaging of synapses with optogenetic stimulation of the LC during learning and memory tasks would be a powerful way of addressing some of these questions.

LIST OF ABBREVIATIONS

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AMPA</td>
<td>α-amino-3-hydroxyl-5-methyl-4-isoxazole-Propionate</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>EPSP</td>
<td>Extracellular Postsynaptic Potential</td>
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<td>ERK</td>
<td>Extracellular-Signal Regulated Kinase</td>
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<td>G-protein</td>
<td>Guanine Nucleotide-Binding Regulatory Protein</td>
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<td>HFS</td>
<td>High-Frequency Stimulation</td>
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<td>LC</td>
<td>Locus Coeruleus</td>
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<td>Low-Frequency Stimulation</td>
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<td>Long-Term Depression</td>
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<td>mTOR</td>
<td>Mammalian Target of Rapamycin</td>
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<td>NA</td>
<td>Noradrenaline</td>
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<td>NMDA</td>
<td>N-Methyl-D-Aspartate</td>
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<td>NST</td>
<td>Nucleus of the Solitary Tract</td>
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<td>PKA</td>
<td>cAMP-Dependent Protein Kinase</td>
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<td>STM</td>
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<td>α-AR</td>
<td>Alpha-Adrenergic Receptor</td>
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<td>β-AR</td>
<td>Beta-Adrenergic Receptor</td>
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CONFLICT OF INTEREST

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