Neuromodulation of Hippocampal Synaptic Plasticity, Learning, and Memory by Noradrenaline

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Abstract: Neuromodulators are chemical substances that modify neural responses without directly triggering synaptic excitation. They broadly impact multiple brain functions, such as arousal, sleep, attention, perception, learning, and memory. The noradrenergic neuromodulatory system widely innervates the mammalian brain, including the hippocampus. Hippocampal synaptic plasticity is believed to importantly contribute to the formation and consolidation of some types of memory. Stimulation of noradrenergic receptors in the hippocampus alters neuronal excitability and synaptic plasticity, suggesting a key role for noradrenaline (NA) in learning and memory. Consistent with this notion, NA enhances memory for a variety of hippocampus-dependent tasks. The effects of NA receptor activation on cellular plasticity may account for NA-dependent modulation of memory in the hippocampus. Furthermore, dysfunction of the noradrenergic neuromodulatory system contributes to numerous cognitive and psychiatric disorders. Determining how NA influences information processing at cellular and behavioural levels is essential for understanding the physiology of memory. Such understanding may also reveal new strategies to improve treatments for human memory disorders.

Keywords: Noradrenaline, hippocampus, neuromodulation, synaptic plasticity, LTP (long-term potentiation), memory, Alzheimer's Disease, posttraumatic stress disorder.

INTRODUCTION

Neuromodulatory systems regulate complex brain functions. Neurons from discrete nuclei in the brain stem can influence the entire central nervous system (CNS) via the diffuse release of neuromodulators. Although much is known regarding the pharmacology and basic physiology of these neuroactive substances, the mechanisms by which they contribute to higher cognitive processes are unclear.

How individual neurons generate a unified percept that can be remembered and recalled is similarly unclear. However, significant progress has been made toward elucidating cellular correlates for the acquisition and retention of memories. Synaptic plasticity, measured as alterations in the strength of neural connections, fulfills many of the criteria for a mechanism that contributes to information storage [1-3]. In the hippocampus, a brain region crucial for long-term memory, synaptic plasticity is well correlated with some types of memory [4-6]. Because the hippocampus is also densely innervated by neuromodulatory neurons, it is an excellent preparation in which to investigate the roles of neuromodulators in synaptic plasticity.

Noradrenaline (NA) is a neuromodulator that can influence both synaptic plasticity and memory. The hippocampus receives significant noradrenergic input, and endogenous release of NA induces some forms of hippocampal synaptic plasticity [7,8]. Furthermore, specific hippocampus-dependent memory processes are impaired in the absence of NA [9,10]. In this review we will focus on the effects of NA release on plasticity and memory in the mammalian hippocampus, tracing these effects from cellular mechanisms to behavioural processes. Within this framework we speculate on how the noradrenergic neuromodulatory system could interact with neuronal activity to influence the physiology and pathology of memory.

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1. NEUROMODULATION

Direct communication between neurons is accomplished by chemical synaptic transmission across synapses. Neuroactive agents involved in synaptic transmission are thought to mediate brief, spatially restricted, postsynaptic responses. However, some of these agents can also pre- or postsynaptically modulate neuronal responses without directly evoking postsynaptic potentials. This type of synaptic action is loosely classified as "neuromodulation." In general, neurotransmitters act through ligand-gated ion channels, whereas neuromodulators act through intracellular second messenger cascades to give slower, longer-lasting, and more spatially diffuse responses [11]. This distinction is becoming blurred with the discovery that specific neurochemicals can elicit effects either as fast neurotransmitters or through slower neuromodulatory mechanisms. Regardless of terminology, neuromodulators are responsible for numerous cellular responses that contribute to normal and pathological brain physiology.

2. NORADRENALINE ANABOLISM AND CATABOLISM

NA was first recognized as a potential neurotransmitter and neuromodulator in the central nervous system in 1954

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[12]. Subsequently, it was found to modulate various cellular responses in neurons and has been implicated in multiple functions at the behavioural and neural systems levels.

NA, like dopamine (DA) and adrenaline, is a catecholamine comprised of an ethylamine group attached to a catechol ring (Fig. **1**). A common biosynthetic pathway, beginning with the amino acid precursor tyrosine, is used to manufacture these neurochemicals [13]. The rate-limiting step in central NA synthesis is the enzyme tyrosine hydroxylase. Importantly, tyrosine hydroxylase activity is regulated by protein kinase C (PKC), cAMP-dependent protein kinase (PKA) and calcium-calmodulin-dependent kinase (CAMK II), allowing for short-term alterations in rates of NA synthesis [14]. Release occurs presynaptically by calcium-dependent exocytosis, and it is regulated primarily by presynaptic autoreceptors that can monitor concentrations of catecholamines at the synapse [15]. Once NA is released at synapses, local inactivation of NA is accomplished by efficient membrane transport-mediated reuptake. The enzymes monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) degrade NA into its corresponding aldehyde to terminate transmitter action [16].

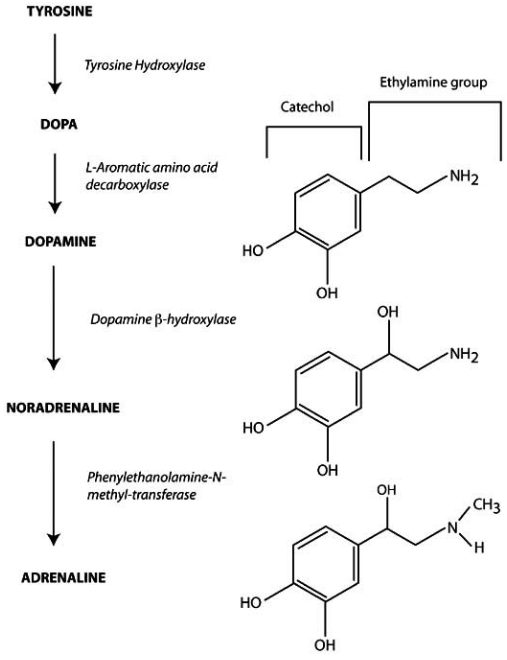

Fig. (1). Primary synthesis pathway for dopamine, noradrenaline, and adrenaline.

3. NORADRENERGIC PATHWAYS IN THE MAMMALIAN BRAIN

Noradrenergic cell bodies are located primarily in the locus coeruleus (LC) and lateral ventral tegmental fields [16]. The LC is a compact nucleus found bilaterally in the caudal pons. It projects widely throughout the cerebral cortex, midbrain, cerebellum, and spinal cord [17], with dense innervation in the thalamus, amygdala and hippocampus [18]. Furthermore, axons from the LC branch out as they reach their target regions to innervate numerous cortical and subcortical structures [19].

The lateral ventral tegmental fields contain more diffusely scattered noradrenergic neurons. Axons from these neurons intermingle with those from the LC and may specifically innervate the basal forebrain regions, including the amygdala and septum [16,20]. The diverse projections of the noradrenergic neuromodulatory system support a role for NA in global information processing mediated by coordinated cellular effects in several brain regions [21].

4. NORADRENERGIC RECEPTOR SUBTYPES

Specific membrane receptors on effector cells bind NA and consequently trigger physiological responses (Fig. **2**). NA receptors belong to a large family of receptors that couples to guanine nucleotide-binding regulatory proteins (G-proteins) to initiate intracellular signaling. However, activation of NA receptors can produce very different intracellular effects depending on characteristics of the stimulated receptor. Based on these effects, receptors are broadly classified as $\alpha 1-, \alpha 2$-adrenergic and β-adrenergic. How activation of these divergent receptor types is coordinated to generate a physiological or behavioural outcome remains highly speculative. Furthermore, activation of NA receptors can modify the properties of hippocampal neurons by persistently altering cellular excitability, and by eliciting synapse-specific changes. Synaptic forms of plasticity, including long-term potentiation (LTP) and long-term depression (LTD), are strongly associated with learning and memory in the mammalian brain [22,23]. Persistent changes in cellular excitability are also linked to some forms of learning, and are thought to operate synergistically with synaptic forms of plasticity [24]. The response of hippocampal neurons to NA release is likely determined by a combination of excitability and synaptic effects.

4.1. α1-Adrenergic Receptors

α1-adrenergic receptors are distributed throughout the CNS. Subclassification of this adrenoceptor based on physiological actions and affinity for various pharmacological agents yields α_{1A}, α_{1B}, and α_{1D} receptor subtypes [25]. These receptor subtypes are expressed to varying degrees in the hippocampus [26,27]. Specifically, mRNA for the $\alpha_{1A/D}$ receptors is present in the pyramidal neurons of the CA1–CA4 fields, and the hilar and granular neurons of the dentate gyrus [27,28]. Human studies have revealed a more precise distribution of α1-adrenergic subtypes. Receptors are restricted to area CA3 and the dentate gyrus, with α_{1A}-adrenergic receptors concentrated in area CA3 and α_{1B}-adrenergic receptors localized mostly in the molecular layer of the dentate gyrus [29]. α1-adrenergic receptors are also found in glia [30], and in populations of interneurons, where they appear to colocalize with somatosatin [31].

In general, α1-adrenergic receptors couple to the Gq/G11 form of G-protein. Activating this G-protein initiates signaling through phospholipase C, resulting in the production of the second messengers diacyglycerol (DAG) and inositol triphosphate (IP3). These second messengers mediate diverse effects on cellular metabolism. Importantly, both DAG and IP3 can increase intracellular calcium levels [32,33].

Because α1-adrenergic receptors are expressed in multiple cell types in the hippocampus, activation of α1-adrenergic

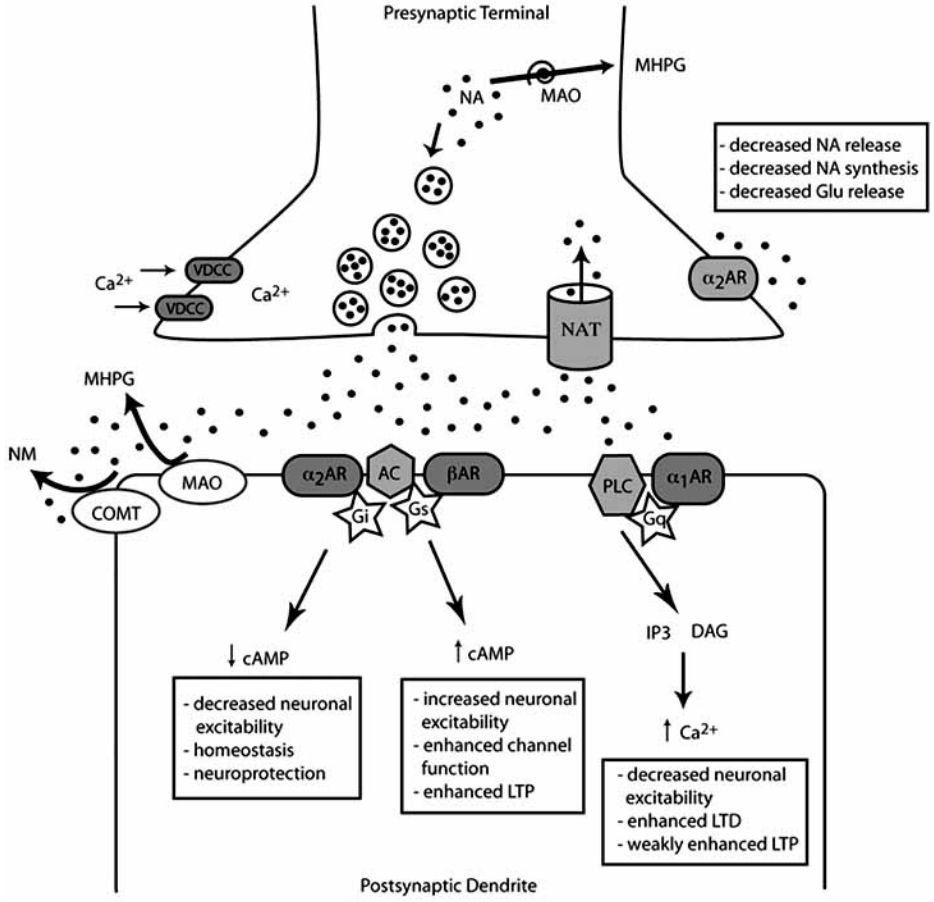

Fig. (2). Schematic of a noradrenergic nerve terminal. NA is released into the synaptic cleft and interacts with α1, α2 and β receptors. Presynaptic α2 receptors regulate the synthesis and release of NA, whereas postsynaptic receptors mediate various cellular responses. Action of NA is terminated by reuptake through NAT, and metabolic degradation by MAO and COMT. VDCC: voltage-dependent calcium channel; AR: adrenergic receptor; NAT: plasma membrane noradrenaline transporter; MHPG: 3-methoxy-4-hydroxy phenethylene glychol; NM: normetanephrine; AC: adenylyl cyclase. Modified from [16].

receptors can generate a variety of cellular effects depending on the target cell population.

4.1.1. Principal Neurons

Excitability

Activation of α1-adrenergic receptors decreases the excitability of principal neurons in the dentate gyrus [34], area CA3 [35], and area CA1 [36] of the hippocampus. This lowered propensity to fire action potentials is often evident as decreased amplitude of the extracellular population spike. The α1-adrenergic receptor-mediated hyperpolarization of principal neurons may result at least partially from activation of inhibitory interneurons. However, there is some evidence that α1-adrenergic receptors can transiently potentiate the amplitude of the population spike in the dentate gyrus *in vivo* [37].

Interestingly, endogenous release of NA from the LC initially suppresses activity of pyramidal neurons before activating them. α1-adrenergic receptors are responsible for the period of suppression, whereas β-adrenergic receptors are responsible for the period of activation [38]. This biphasic sequence of inhibition-excitation may be related to *in vitro* observations that high concentrations of applied NA decrease pyramidal cell excitability, presumably by preferential activation of α1-adrenergic receptors. Correspondingly, lower concentrations of NA increase excitability, resembling β-adrenergic receptor activation [36,39,40]. It is possible that varying concentrations of NA in the synaptic cleft allow α1- and β-adrenergic effects to predominate during different patterns of release.

Synaptic Plasticity

The effects of α1-adrenergic receptors on synaptic plasticity in the hippocampus are generally weak and indirect. These responses vary depending on the hippocampal subregion. In the dentate gyrus, α1-adrenergic agonists do not produce consistent changes in the slope of the extracellular postsynaptic potential (EPSP) *in vivo* [37].

In area CA3, presynaptic α1-adrenergic receptors are involved in presynaptic inhibition. Application of NA decreases release of glutamate (Glu) from presynaptic terminals, and this effect is blocked by an α1-adrenergic receptor antagonist [41]. Because LTP at the mossy fibre synapses has a presynaptic locus [42,43], these receptors could affect LTP induction in this subregion.

Activation of α1-adrenergic receptors mediates diverse responses in area CA1. α1-adrenergic agonists subtly facilitate LTP induction and maintenance when paired with weak electrical tetanus [44,45]. The effects of NA on stability of LTP in area CA1 also have an α1-adrenergic component. NA application prevents the reversal, or depotentiation, of LTP by low-frequency stimulation (LFS). Activation of both α1- and β-adrenergic receptors is required to generate this immunity to depotentiation [46].

These weak α1-adrenergic effects could be explained by evidence suggesting that α1-adrenergic activation can either antagonize or potentiate β-adrenergic effects based on interactions with subtypes of adenylyl cyclase. α1-adrenergic receptor activation alone produces no change, or a decrease in levels of cAMP. However, co-activation of α1- and β-adrenergic receptors can increase adenylyl cyclase activity [47]. The subtle effects of α1-adrenergic receptors on LTP in CA1 could result from concurrent β-adrenergic receptor activation.

α1-adrenergic receptors are also involved in LTD in area CA1. Application of high concentrations of NA or α1-adrenergic agonists induces a persistent decrease in synaptic strength [48]. The mechanism responsible for this synaptic response is unknown, but could include IP3-mediated calcium transients.

4.1.2. Glia

Glial cells can influence synaptic transmission and contribute to some forms of synaptic plasticity [49]. Activation of α1-adrenergic receptors induces calcium transients in hippocampal astrocytes [50], suggesting that α1-adrenergic receptors regulate synaptic function by affecting these non-neuronal cells. Possible outcomes of astrocytic calcium flux include buffering of potassium, neurotransmitter uptake or release, and alterations in gene expression [50].

4.1.3. Interneurons

Application of NA to area CA1 causes an α1-adrenergic receptor-dependent depolarization of interneurons in all cell layers [51,52]. Because many of these interneurons make synaptic connections throughout stratum pyramidale, they could potentially influence firing rates of pyramidal neurons [51]. Furthermore, activation of α1-adrenergic receptors on glutamatergic afferents to interneurons depresses feed-forward inhibition [53]. Functionally, interneurons often respond to several neuromodulators, indicating that interactions between neuromodulatory systems can regulate these inhibitory networks [52].

4.2. α2-Adrenergic Receptors

Based on sensitivity to pharmacological agents and tissue distribution, α2-adrenergic receptors can be further divided into α_{2A}, α_{2B}, and α_{2C} receptor subtypes [25]. The hippocampus contains roughly similar α_{2A} and α_{2C} receptor expression, whereas α_{2B} receptors are restricted to the diencephalon [54-56]. The distribution of α_2 receptors is similar throughout all hippocampal subregions, with receptors localized predominantly presynaptically. However, some receptor expression is observed in dendritic spines of pyramidal and granule cells, as well as in glial processes [57]. Therefore, several possible sites for α_2-adrenergic receptor-mediated effects exist.

The α_2-adrenergic receptor couples to the inhibitory G-protein Gi to reduce adenylyl cyclase activity and subsequently decrease intracellular cAMP [58-60]. In general, this signaling inhibits the electrical activity of pyramidal neurons. α_2-adrenergic agonists applied microiontophoretically to hippocampal areas CA1 and CA3 strongly suppress firing of pyramidal neurons [61]. Studies examining endogenous NA release elicited by stimulation of the LC suggest that postsynaptic α_2-adrenergic receptors exert this suppressant effect extrasynaptically [38].

However, α_2-adrenergic effects on hippocampal plasticity are primarily presynaptically mediated. Presynaptic α_2-adrenergic autoreceptors are the main regulators of NA release, preventing further release when bound by NA diffusing from the synaptic cleft [15]. Additional signal transduction mechanisms may be recruited by α_2-adrenergic receptors to fulfill this function, because α_2-adrenergic-mediated inhibition of transmitter release is insensitive to the inactivation of Gi proteins [16].

α_2-adrenergic receptors are also involved in presynaptic inhibition of other neurotransmitters. Application of α_2-adrenergic receptor agonists decreases excitatory Glu currents by reducing presynaptic Glu release [62]. This effect is blocked by inactivation of Gi/o proteins, and is mediated by a reduction in Ca^{2+} currents through voltage-gated calcium channels [62].

Overall, α_2-adrenergic receptors appear to be critical for homeostatic and neuroprotective functions in the hippocampus, rather than mediating direct effects on synaptic plasticity. α_2-adrenergic receptors are implicated in inhibition of the spread of epileptic activity [63] and protection during cerebral ischemia [64]. Coupled with their suppressant effect on hippocampal pyramidal cells, these receptors could prevent neurotoxicity associated with excessive cell firing and release of excitatory neurotransmitters.

4.3. β-Adrenergic Receptors

β-adrenergic receptors are classified into β1-, β2- and β3-adrenergic subtypes based on differential potency of agonists. The agonist isoproterenol activates β1- and β2-adrenergic receptors more strongly than endogenous NA or adrenaline whereas β3-adrenergic receptors respond most strongly to NA. Furthermore, adrenaline is more potent than NA at β2-adrenergic receptors only [16].

Expression of β-adrenergic receptors in the central nervous system is localized to the cerebral cortex, hippocampus, thalamus and cerebellum [65,66]. In the human brain, the concentration of β-adrenergic receptors is highest in the subregions of the hippocampus [67]. β1- and β2-adrenergic receptors are localized in pyramidal cells and dentate granule cells, with β2-adrenergic receptor mRNA more prevalent than β1-adrenergic receptor mRNA. Whereas interneurons generally do not express β-adrenergic receptors [65,68], isolated astrocytes in CA1 predominantly contain β2-adrenergic receptors [69]. Evidence of functional β3-adrenergic receptors in this brain region is lacking [68,70]. β-adrenergic receptors may therefore potently and directly affect plasticity

in the hippocampus based on their primary association with the principal neurons in hippocampal subregions.

β-adrenergic receptors couple to the Gs form of G-protein to mediate intracellular signaling [71,72]. Gs proteins stimulate adenylyl cyclase activity to increase levels of cAMP [73]. Correspondingly, application of selective β-adrenergic agonists induces an accumulation of cAMP in multiple brain regions. This β-adrenergic response involves primarily β1-adrenergic receptors in the cerebral cortex and hippocampus; a more significant β2-adrenergic contribution is observed in the cerebellum [74]. Through increases in intracellular cAMP, β-adrenergic receptors importantly modulate numerous processes involved in plasticity.

4.3.1. Channel Function

Functional modulation of gated membrane channels underlies some forms of hippocampal synaptic plasticity [75,76]. Stimulating β-adrenergic receptors during excitatory synaptic transmission can increase the influx of calcium into the postsynaptic cell through NMDA receptors [77]. This influx of calcium is critical for the initiation of signaling through intracellular kinase cascades such as PKC and CAMKII [78]. β-adrenergic receptors further regulate calcium dynamics in dendrites by altering the properties of voltage-dependent calcium channels (VDCCs) [79-81]. Application of β-adrenergic agonists enhances the activity of VDCCs in the dentate gyrus, area CA3, and area CA1 of the hippocampus [80-82]. Some evidence suggests that β-adrenergic receptor activation may also prevent the delayed facilitation of L-type VDCCs, contributing to the β-adrenergic receptor-mediated inhibition of the slow after-hyperpolarization current [79]. Thus, β-adrenergic receptors play a key role in the temporal dynamics of calcium flux in dendrites of hippocampal neurons.

Furthermore, β1-adrenergic-activated signaling modulates AMPA receptor function by phosphorylation of the GluR1 subunit [83,84]. This subunit is critically involved in LTP [85,86], and its regulation by β1-adrenergic receptors highlights the potential importance of these receptors to homosynaptic plasticity [87]. β-adrenergic receptors also decrease spike frequency adaptation by blocking calcium-activated potassium channels that contribute to the after-hyperpolarization current [47,88,89]. The resulting increase in excitability of hippocampal neurons may underlie the ability of NA to enhance attention and arousal [90].

4.3.2. Receptor Desensitization

β-adrenergic receptors can also desensitize. PKA and β-adrenergic receptor kinase can phosphorylate β-adrenergic receptors and uncouple them from their associated Gs-protein. The receptor is then bound by β-arrestin, which competes with the Gs-protein and blocks activation of adenylyl cyclase. Internalization and sequestration of these uncoupled β-adrenergic receptors reduces the cellular response to NA or applied agonists [16]. Desensitization is particularly important in the noradrenergic neuromodulatory system because chronic administration of some psychiatric drugs affects endogenous levels of NA and its receptors [91,92].

4.3.3. Excitability

Activation of β-adrenergic receptors generally increases the excitability of principal neurons in the dentate gyrus, area CA3, and area CA1 of the hippocampus. In the dentate gyrus, application of NA or a β-adrenergic agonist causes long-lasting potentiation of the population spike, and NA depletion decreases the amplitude of the population spike [93-95]. The effects of β-adrenergic receptor activation in this subregion are also pathway specific. β-adrenergic receptor-mediated potentiation is observed in the medial perforant path, whereas β-adrenergic receptor-mediated depression is seen in the lateral perforant path [96]. These pathways are histochemically and anatomically distinct, suggesting that differential effects of NA in this subregion may be important for selective information processing [96,97].

Endogenous NA release from the LC similarly enhances cellular excitability in the dentate gyrus [98,99], and this response is mediated by both α– and β-adrenergic receptors [37]. Interestingly, blockade of β-adrenergic receptors during high frequency electrical stimulation prevents LTP of the EPSP slope, but not potentiation of the population spike [100]. This indicates that β-adrenergic receptors can differentially affect specific components of plasticity.

β1-adrenergic receptors also enhance potentiation of the pyramidal cell population spike in areas CA3 and CA1 [39,101-103]. This increased cellular excitability increases the frequency of spontaneous bursts in area CA3 [103], potentially facilitating the auto-associative properties of this hippocampal subregion [11].

5. β-ADRENERGIC RECEPTORS AND SYNAPTIC PLASTICITY

LTP and LTD are importantly linked to memory function in the mammalian brain [22,23]. Parallel to their aforementioned effects on cellular excitability, β-adrenergic receptors also strongly modulate synaptic plasticity in all hippocampal subregions. However, the specific cellular responses elicited often depend on the histology, cellular circuitry, and biochemical properties of the subregion in question (Fig. **3**).

5.1. Dentate Gyrus

LTP generated by high frequency electrical stimulation (HFS) requires β-adrenergic receptor activation in the dentate gyrus [100,104]. Application of a β-adrenergic antagonist prevents induction of LTP in the medial and lateral perforant paths [104]. However, β-adrenergic receptor blockade inhibits only HFS-induced potentiation of the EPSP, without affecting potentiation of the population spike [100]. This dichotomy suggests that distinct mechanisms underlie potentiation of synaptic strength and cellular excitability.

Paralleling β-adrenergic receptor-mediated alterations in population spike amplitude, application of NA or β-adrenergic agonists induces long-lasting potentiation of EPSPs in the medial perforant path, and long-lasting depression of EPSPs in the lateral perforant path [96,105]. This plasticity requires activation of NMDA receptors, but not electrical activation of afferent neurons [105].

Initial *in vivo* studies failed to find alterations in synaptic strength in response to NA or LC activation [93,98,106]. However, this discrepancy may be caused by the selective enhancement of long-term, but not short-term, plasticity by NA *in vivo*. Stimulation of the LC potentiates EPSPs 24 hours, but not 3 hours, later [8]. Similarly, activation of the basolateral amygdala causes a β-adrenergic receptor-mediated increase in LTP maintenance in the dentate gyrus [7]. This late-phase potentiation is dependent on new protein synthesis [7,8], a key characteristic of stable forms of LTP and long-term memory [107-109].

5.2. Area CA3

LTP in area CA3 is β-adrenergic receptor-dependent. Blockade of these receptors during HFS prevents early and late phases of LTP [110]. Correspondingly, application of NA or β-adrenergic agonists elicits a frequency-dependent increase in the magnitude, duration and induction probability of LTP [111,112]. During LFS, activation of β-adrenergic receptors has little effect on synaptic strength at synapses with incoming mossy fibres [111,112]. Similarly, pairing β-adrenergic receptor activation with LFS at associational-commissural CA3 synapses does not induce plasticity [113] (Fig. **3**).

However, applying a β-adrenergic agonist during weak tetanus increases the likelihood for LTP induction, and increases LTP expression. Electrical stimuli that are subthreshold for LTP induction are able to generate LTP when β-adrenergic receptors are activated. β-adrenergic receptors also elicit late-phase LTP when paired with stimulation protocols that normally induce early-phase LTP [110]. Therefore, β-adrenergic receptor activation can modulate properties of LTP, but cannot increase synaptic strength without concurrent high frequency stimulation.

The mechanism for this modulation of LTP is thought to be presynaptic [110], consistent with studies demonstrating that HFS and forskolin-dependent LTP is presynaptically mediated in this subregion [42,43,114]. In this manner, endogenous actions of NA on mossy fibre presynaptic terminals could increase excitatory transmitter release and enhance initial expression of LTP [110].

5.3. Area CA1

Unlike other hippocampal subregions, β-adrenergic receptors in area CA1 are not required for the induction of LTP by HFS [10,115-117]. Activation of β-adrenergic receptors during multiple trains of HFS generates late-phase LTP that does not differ in either induction or maintenance from LTP elicited by HFS alone (JN Gelinas, unpublished observations). Similarly, application of β-adrenergic agonists to area CA1 does not persistently alter basal synaptic strength [118,119]. These studies suggest that the role of β-adrenergic receptors in this hippocampal subregion is distinct from their role in the dentate gyrus and area CA3.

Conversely, β-adrenergic receptor activation importantly modulates the effects of LFS on synaptic strength. Long trains of LFS appear to activate protein phosphatases [119-121] that oppose LTP induction and depress synaptic strength [122]. Pairing this LFS with activation of β-adrenergic receptors overcomes the phosphatase-mediated inhibition and permits induction of LTP [118,119,123] (Fig. **3**). Induction of this LTP is dependent on the β1-adrenergic receptor, and requires PKA and extracellular-signal regulated kinase (ERK) signaling cascades [119,123,124].

Bursts of action potentials known as "complex spikes" could enhance LTP induction during β-adrenergic receptor activation. *In vivo*, CA1 pyramidal cells fire complex spikes that are critical to plasticity [125,126]. Complex spikes also facilitate the generation of LTP by particular patterns of LFS *in vitro* [127]. β-adrenergic receptor activation during LFS doubles the amplitude of these complex spikes in a PKA-dependent manner [128], potentially amplifying the postsynaptic depolarization elicited by weak electrical stimulation and permitting induction of LTP. Furthermore, β-adrenergic receptor-mediated enhancement of LTP induction is observed during theta-burst stimulation, a protocol that mimics the *in vivo* firing pattern of pyramidal cells seen during spatial exploration in rodents [117,129].

Activation of β-adrenergic receptors also influences the maintenance of LTP. Pairing β-adrenergic receptor activation with electrical stimulation that normally cannot induce long-lasting LTP generates persistent LTP that is dependent on protein synthesis and ERK signaling [118]. Whereas β-adrenergic receptor activation in area CA3 enhances the expression of LTP to a degree dependent on the amount of synaptic stimulation applied [110], β-adrenergic receptor activation in area CA1 converts subthreshold stimulation to L-LTP directly [118]. Signaling through ERK and mammalian target of rapamycin (mTOR, a kinase) that subsequently stimulates dendritic protein synthesis may underlie the increased stability of β-adrenergic receptor-mediated LTP in this subregion. However, pairing β-adrenergic receptor activation with theta-burst stimulation does not enhance the maintenance of LTP [117]. Interestingly, rats lesioned with a specific neurotoxin of the catecholamine system demonstrate decreased maintenance of theta-burst LTP in area CA1 [130]. Thus, this stimulation protocol recruits noradrenergic input and cannot be further enhanced by application of a β-adrenergic agonist.

Neuromodulators such as NA can influence the 'state' of a synapse, altering its response to future stimulation. This plasticity process is known as "metaplasticity" [131]. Activation of naïve synapses with certain stimulation protocols induces LTP, and also initiates a metaplastic process that prevents further LTP induction by the same pattern of stimulation [132,133]. Application of a β-adrenergic agonist can inhibit this metaplastic process, and permit subsequent induction of LTP at previously activated synapses [134]. Concurrent activation of α- and β-adrenergic receptors also prevents the activity-dependent reversal, or depotentiation, of LTP [46]. Furthermore, the time window for associative LTP is enhanced by activation of β-adrenergic receptors [135]. Taken together, these studies suggest that NA acting through β-adrenergic receptors can also engage metaplastic processes to decrease the threshold for future induction of LTP.

The concentration of applied NA appears to determine whether α- or β-adrenergic plasticity processes are engaged. Low concentrations of NA preferentially activate β-

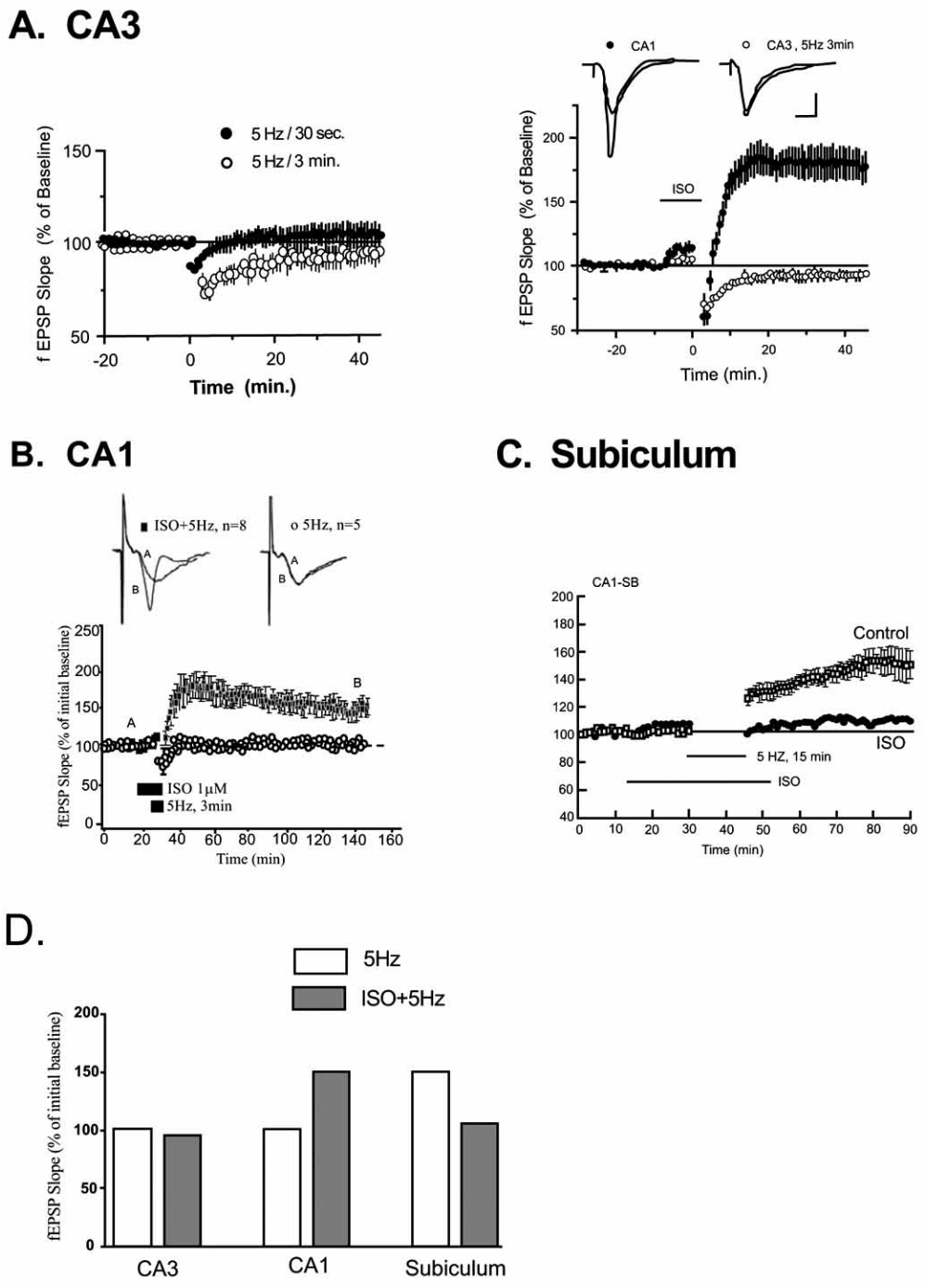

Fig. (3). β-adrenergic receptors differentially modulate synaptic plasticity in hippocampal subregions. A. 5 Hz LFS in area CA3 does not persistently alter synaptic strength (open circles, left panel), and pairing application of ISO with LFS does not alter this response (open circles, right panel). B. 5 Hz LFS in area CA1 does not persistently alter synaptic strength (open circles), whereas pairing application of ISO with LFS induces long lasting LTP (filled squares). C. 5 Hz LFS in the subiculum induces LTP (open squares), and pairing application of ISO with LFS prevents LTP induction. D. Summary histogram comparing the synaptic responses with and without ISO application 40 min after LFS in each subregion. Part (A) reprinted from [112], Copyright 1998 with permission from Elsevier; Part (B) reprinted from [117], Copyright 2005 with permission from the Society for Neuroscience; Part (C) reprinted from [136], Copyright 2005 with permission from the National Academy of Sciences, U.S.A.

adrenergic receptors. At these concentrations, NA blocks the induction of LTD by certain patterns of LFS and decreases the threshold for LTP induction, mimicking effects of β-adrenergic agonists [46 JN Gelinas, unpublished data]. Higher concentrations of NA elicit α-adrenergic receptor-dependent LTD [48], highlighting the finely tuned antagonistic interaction of α- and β-adrenergic receptors in this subregion.

5.4. Subiculum

Few studies have examined plasticity in the CA1-subiculum pathway [136]. Activation of β-adrenergic receptors in this subregion facilitates the induction of LTP by electrical stimulation that can induce LTD in other hippocampal subregions, and prevents induction of LTP by higher frequency electrical stimulation [137](Fig. **3**). This frequency dependence may reflect high endogenous stimulation of β-adrenergic receptors by LTP-inducing stimuli. Exogenous application of β-adrenergic agonists therefore saturates this β-adrenergic receptor-dependent mechanism and inhibits LTP induction [137]. Shifts in β-adrenergic neuromodulation of plasticity in the hippocampus could reflect differences in subregional functions and the processing of information within the hippocampal trisynaptic circuit.

5.5. Summary

As described above, release of NA in the hippocampus can modify numerous cellular parameters involved in generating synaptic plasticity. NA also acts on different hippocampal cell types, including principal cells, interneurons, and glia. It is therefore unlikely that NA modulates cellular plasticity by means of a single physiological mechanism. Instead, NA may contribute to the complexity of information processing by recruiting several mechanisms in response to specific cellular stimuli. For instance, activation of β-adrenergic receptors in area CA1 of the hippocampus enhances cellular excitability and promotes complex spike bursting in pyramidal cells [123]. Concurrently, activated β-adrenergic receptors recruit PKA and ERK signaling cascades to increase calcium influx through NMDA receptors and inhibit potassium channels, respectively [77,138]. LTP is only generated when appropriate cellular firing patterns are paired with these synaptic channel modifications, allowing for sophisticated coincidence detection [139]. Similar combinations of intracellular mechanisms may govern various NA receptor-dependent effects, allowing physiological responses to vary depending on the behavioural situation in which NA release is elicited.

6. COGNITIVE EFFECTS OF NORADRENALINE IN THE HIPPOCAMPUS

It has been proposed that the cardinal purpose of noradrenergic neuromodulation is to facilitate the rapid reorganization of neural networks in response to contexts that require cognitive and behavioural shifts [140]. The physiological mechanisms responsible for achieving this general function, and the specific outcomes observed, most likely depend on the brain region and cognitive process being considered. Because the hippocampus is involved in memory processing, release of NA in this brain region may modulate the parameters for acquisition, storage, or retrieval of memory. On a physiological level, NA could therefore affect the alterations in synaptic strength that are hypothesized to underlie learning and memory. Release of NA has been shown to influence multiple aspects of plasticity, including cellular excitability, induction and maintenance of LTP, and metaplasticity. How these distinct physiological mechanisms interact to create a coherent, observable modulation of memory remains mostly speculation. Here, we describe the effects of NA on the hippocampal memory systems, and consider the underlying mechanisms that may contribute to these effects.

6.1. Declarative Memory

The hippocampus is critical for creating new memories of facts, events, and places that can be consciously recalled and expressed explicitly [141,142]. This declarative memory is often assessed in laboratory animals by screening their performance on spatial and associative memory tasks. NA has been found to enhance memory for a variety of hippocampus-dependent tasks.

6.1.1. α-Adrenergic Receptors

α1-adrenergic receptors make small, but measurable, contributions to hippocampal memory [33,143]. Application of α1-adrenergic receptor agonists subtly facilitates acquisition of the spatial water maze task in rats [144,145]. However, this enhancement is possibly due to an alteration in strategy rather than increased memory [33]. Furthermore, effects of α1-adrenergic antagonists are often observable only in the presence of other neuromodulatory or neurotransmitter deficits [146,147]. On a cellular level, the ability of α1-adrenergic receptor activation to facilitate increases in cAMP downstream of β-adrenergic receptors could explain these milder, synergistic effects on memory function.

Conversely, up-regulation of α2-adrenergic receptors actually decreases performance on spatial memory tasks. Constitutive activity of α2-adrenergic receptors in the hippocampus produces deficits in spatial navigation in the water maze [148]. It is possible that increasing α2-adrenergic receptor–mediated presynaptic inhibition interferes with hippocampal memory processes.

6.1.2. β-Adrenergic Receptors

Activation of β-adrenergic receptors accounts for the majority of NA-dependent memory effects. Injection of β-adrenergic receptor antagonists into the hippocampus inhibits memory for spatial water maze tasks [9] and contextual fear conditioning [149]. Similarly, administration of these antagonists in acute or chronic doses inhibits spatial and associational memory [150-152]. Intracellular signaling via the cAMP-PKA cascade in the hippocampus may mediate these responses downstream of the β-adrenergic receptor [153,154].

Signaling through β-adrenergic receptors affects specific temporal phases of memory. These receptors are implicated in long-term (LTM), rather than short-term (STM), memory processes. NA injected into area CA1 of the hippocampus selectively enhances LTM without altering STM [155], an effect that is mimicked by infusion of drugs that stimulate PKA [153]. Post-conditioning β-adrenergic receptor blockade also impairs LTM for contextual fear conditioning [149] (Fig. **4**). Furthermore, β-adrenergic antagonists inhibit LTM for an associative task when applied two hours after training, suggesting a role in a late-phase of memory storage [152]. Based on these temporal requirements for β-adrenergic receptor activation, a role for the noradrenergic system in memory consolidation has been suggested [156,157]. Some studies, however, did not find evidence for β-adrenergic receptor-dependent memory consolidation and suggest that noradrenergic neuromodulation is not generally necessary

for memory consolidation [158,159]. Interpretation of these behavioural data is complicated by the fact that extended training time was required for some tasks, during which memory may be repeatedly acquired, consolidated, retrieved, and reconsolidated [10].

Because time courses for temporal phases of memory can vary depending on the behavioural task used, memory processing is often defined by acquisition, consolidation, and retrieval stages. These stages may selectively recruit specific brain regions and molecular mechanisms, allowing for better isolation of different memory processes [160]. There is some evidence to suggest that NA acts through β-adrenergic receptors in the hippocampus to mediate retrieval of memories [10,161,162]. Stimulation of the LC or injection of NA into the hippocampus promotes retrieval of memory for food-motivated maze and inhibitory avoidance tasks [161,162].

However, these studies did not demonstrate that β-adrenergic receptor activation was *necessary* for retrieval. Mice that are genetically engineered to lack endogenous NA and adrenaline (Dbh $^{-/-}$) have been used to address this issue [10] (Fig. **4**). These mice display impaired contextual fear memory that can be rescued by pre-testing, but not by pre-training, restoration of NA levels. These results can be replicated in rats and for other hippocampus-dependent memory tasks (spatial water maze). Importantly, the NA-dependent effects were shown to require β- but not α-adrenergic receptors [10]. Therefore, in the absence of NA, memories are acquired and consolidated, but cannot be retrieved. However, these Dbh$^{-/-}$ mice lack NA from birth. Because restoration of NA in the mice during both training and testing rescues contextual fear conditioning, this memory deficit is probably not due to a developmental abnormality. Neuromodulatory compensation in other brain systems remains unexplored.

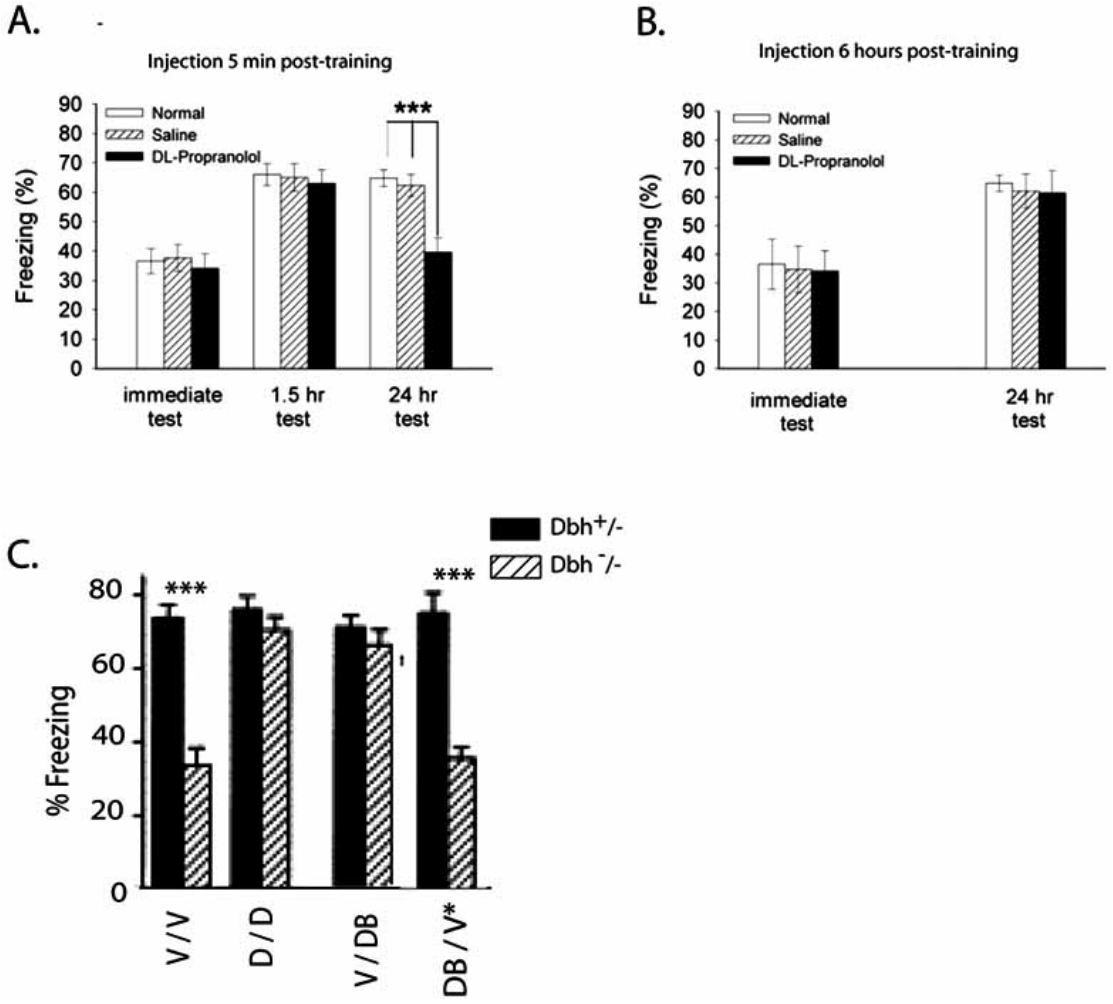

Fig. (4). β-adrenergic receptors and memory – consolidation or retrieval? A. Propranolol injected 5 min after CFC training in normal mice impairs memory 24 hours, but not 1.5 hours after training. B. Propranolol injected 6 hours after CFC training in normal mice does not impair memory 1.5 or 24 hours after training. C. Mice that lack NA/A (Dbh $^{-/-}$) have impaired memory for CFC compared to mice with normal NA/A (Dbh $^{+/-}$). This deficit in Dbh $^{-/-}$ mice can be rescued by pre-testing, but not pre-training, restoration of NA levels. Testing was 24 hours after training, except for DB/V*, which was 48 hours after training to ensure complete absence of NA during testing. These effects were subsequently shown to require β-, but not α-adrenergic receptors. Labels are formatted as "1st/2nd," where 1st is injection before training and 2nd is injection before testing. CFC is contextual fear conditioning; V is vehicle; D is L-DOPS, which can restore NA levels in the Dbh $^{-/-}$ mice; DB is L-DOPS+benserazide, a combination that restricts the restoration of NA levels to central structures. Parts (A) and (B) reprinted from [153], Copyright 2003 by Blackwell Publishing; Part (C) reprinted from [10], Copyright 2004 with permission from Elsevier.

β-adrenergic receptors are also implicated in post-retrieval memory processing. Interestingly, the β-adrenergic receptor-dependency of retrieval is time-limited. One week post-training, memory retrieval is restored in the $Dbh^{-/-}$ mice [10]. This may reflect the transfer of memory from the hippocampus to cortical storage sites [163-165]. Furthermore, blockade of β-adrenergic receptors after the reactivation of a memory induces amnesia when this memory is tested at a later time point [166]. β-adrenergic signaling is also required for the extinction of memory, a process which allows new associations to be made about previously-experienced stimuli [167]. Therefore, β-adrenergic receptors may contribute to the complex, and as yet poorly understood, interactions that ultimately determine the relative strength of stored memories.

6.2. Mechanisms of Declarative Memory

Considerable correlative evidence suggests that long-lasting forms of plasticity represent a cellular mechanism for memory storage in the brain [5,6,23,168]. Because NA importantly modulates both hippocampal synaptic plasticity and hippocampus-dependent memory, it is possible that the effects of NA on a cellular level contribute to its actions on behaviour.

Several types of behaviour can elicit NA-dependent alterations in plasticity. Exposure to novel stimuli elicits spike bursting in LC neurons and a consequent increase in population spike amplitude in the dentate gyrus. This effect can be partially blocked by a β-adrenergic receptor antagonist [169]. Similarly, novelty facilitates a β-adrenergic receptor-dependent reinforcement of LTP in the dentate gyrus [170]. Therefore novel stimuli could recruit the noradrenergic neuromodulatory system to increase information transmission and storage in the hippocampus, creating a behaviourally-mediated "gate" for information storage and consolidation.

The role of NA in LTM is supported by NA-dependent facilitation of long-lasting synaptic plasticity in hippocampal subregions. In areas CA3, CA1 and the subiculum, activation of β-adrenergic receptors enhances LTP induction and maintenance in a frequency-dependent manner [110,118,119, 137]. β-adrenergic receptor-mediated enhancement of LTP stability is associated with recruitment of protein synthesis. Importantly, new protein synthesis is required for the stability of both LTP and LTM [107,108,171]. Application of numerous neuromodulatory agents (including brain-derived neurotrophic factor (BDNF), cholinergic, glutamatergic and β-adrenergic agonists) induces new protein synthesis, often in the dendrites [118,172-174]. Neuromodulators such as NA might engage translation to enhance the potency of stimuli that are initially sub-threshold for associative learning and memory.

Computational models of hippocampal subregion function provide further insight into neuromodulation by NA at the systems level. Area CA3 is thought to be critical for the storage and retrieval of contextual memories, because of its high capacity for autoassociation via excitatory feedback synapses. Area CA1 is proposed to be heteroassociative, comparing memory of context from CA3 with information about current context [11,175,176]. In the absence of endogenous NA, patterns of neuronal activity following exposure to a previously experienced, highly salient environment are normal in area CA3, but not in area CA1 [177]. Thus, the contextual memory retrieval deficits caused by lack of NA may result from defective transmission of information from area CA3 to area CA1.

6.3. Emotional Memory – Hippocampus-Amygdala Interactions

Stress hormones, including NA and adrenaline, are strongly implicated in emotional memory storage. Systemic injection of adrenaline increases retention of inhibitory avoidance tasks [178]. Subsequent studies indicated that peripheral adrenaline mediates this memory enhancement by activating β-adrenergic receptors on vagal afferents in the nucleus of the solitary tract (NST). Noradrenergic projections from the NST innervate forebrain structures and brainstem nuclei, including the amygdala [179-181].

Emotional stimuli also activate the hypothalamic-pituitary-adrenocortical axis, eliciting release of glucocorticoids into peripheral circulation. Glucocorticoids influence numerous memory processes, including memory consolidation [182-184]. The amygdala is a crucial locus of action for glucocorticoid-mediated memory enhancements [185]. Activation of amygdalar glucocorticoid receptors elicits behavioural responses by increasing the potency of noradrenergic signaling via interactions of G-proteins [186].

The facilitatory effects of emotional arousal on memory can therefore be mostly attributed to signaling downstream of noradrenergic receptors in the amygdala. Although activation of α1- and β-adrenergic receptors in the amygdala contributes to memory enhancement, the α1-adrenergic receptor-mediated response requires co-activation of β-adrenergic receptors [187-189]. β-adrenergic antagonists infused directly into the amygdala inhibit memory enhancements caused by peripheral injections of adrenaline [190] or glucocorticoids [191]. Furthermore, studies of human subjects demonstrate that β-adrenergic receptor antagonists selectively prevent the increased retention of memory caused by exposure to emotional stimuli, without affecting memory for neutral stimuli [192,193]. Stimulation of the noradrenergic neuromodulatory system can likewise enhance emotional memory [194].

However, behavioural studies in animals indicate that the amygdala mediates effects on memory by modulating responses in other brain regions. Injection of amphetamine into the hippocampus or caudate nucleus selectively enhances retention for hippocampus- or caudate-dependent memory tasks, respectively. Activation of the amygdala with amphetamine, however, facilitates memory for both hippocampus- and caudate-dependent tasks. Subsequent inactivation of the amygdala prior to retrieval does not prevent expression of the memory enhancements [195]. Thus, the amygdala may promiscuously modulate memory in several brain regions, without functioning as a site for long-term memory storage.

In particular, reciprocal interactions between the amygdala and the hippocampus may be responsible for the facilitation of declarative memory pertaining to emotional material [195]. This facilitation can be assessed in humans

using functional neuroimaging methods. Increased and more highly correlated activity in the amygdala and medial temporal lobe (MTL) during encoding of stimuli predicts enhanced memory for emotional stimuli [196,197]. In patients with epilepsy or MTL sclerosis, the degree of pathology in the hippocampus determines memory for both emotional and neutral material. Pathology of the amygdala selectively impairs memory for emotional materials. Furthermore, encoding activity in the hippocampus for emotional materials is dependent on the degree of amygdalar pathology [198]. These results suggest that the hippocampus and amygdala function cooperatively to acquire emotional memory. Anatomical pathways connecting the amygdala and hippocampus likely convey important information between these brain structures [199].

The retrieval of emotional memory after extended retention intervals is also correlated with increased activity in the amygdala and hippocampus. One year after an encoding session, retention was greater for emotional than neutral stimuli. Successful retrieval of the emotional items augmented activity in the hippocampus and amygdala relative to retrieval of neutral items [200]. The increased signaling efficacy responsible for enhancement of emotional memory shortly after encoding is therefore retained over time, and is operational during memory retrieval.

NA acting through β-adrenergic receptors plays an important role in interactions between the amygdala and hippocampus. Enhancements in episodic memory for emotional words are blocked by application of β-adrenergic receptor antagonists [201]. Furthermore, successful encoding-evoked activation in the amygdala for emotional items is inhibited by β-adrenergic receptor blockade. Recognition of these same emotional items triggers activity in the hippocampus only if β-adrenergic receptors are functional during encoding [202]. Activation of β-adrenergic receptors may therefore mediate the amygdala-dependent modulation of hippocampal memory for emotional stimuli.

6.4. Mechanisms of Emotional Memory

How does noradrenergic activation in the amygdala facilitate memory in other brain regions? The amygdala sends direct projections to the dentate gyrus independent of the perforant path [203], and receives projections from the hippocampus in the ventral angular bundle [204]. Plasticity within these pathways could contribute to observed amygdalar modulation of hippocampal emotional memory. Stimulation of nuclei within the amygdala facilitates LTP induced by tetanization of the perforant path, and lesions of the basolateral amygdala inhibit LTP in the dentate gyrus [205]. Evidence indicates that activity in the amygdala can elicit LTD and LTP in the dentate gyrus, depending on the timing and amount of this activity [206,207]. Importantly, β-adrenergic receptor antagonists infused into the amygdala impair LTP induction in the dentate gyrus, suggesting a central role for NA in the modulation of hippocampal LTP [208,209]. Although HFS delivered to the ventral angular bundle can generate LTP in the basolateral amygdala, the neurochemical requirements of this LTP are mostly unknown [204].

Some evidence suggests that theta activity also contributes to the memory-enhancing effects of amygdalar-hippocampal interactions. Neurons in the amygdala oscillate at theta frequency (4-8Hz) during intense appetitive or aversive arousal [210]. Similarly, high-amplitude theta activity is observed to modulate cellular responses in the hippocampus during arousal and locomotion [211,212]. Simultaneous recordings in the amygdala and hippocampal area CA1 reveal that rhythmically synchronized theta activity occurs between these two brain regions when animals are exposed to a conditioned fear stimulus [213]. This oscillatory activity could promote interactions between the amygdala and hippocampus, potentially via thalamic pathways [214]. Because activation of β-adrenergic receptors during theta frequency stimulation enhances LTP induction [119], amygdala activation could potentiate the hippocampal response to NA. As such, oscillatory activity in the amygdala could facilitate the maintenance of long-lasting plasticity and memory.

7. CLINICAL IMPLICATIONS

The importance of NA for synaptic plasticity and memory suggests that dysfunction of the noradrenergic neuromodulatory system could elicit a variety of cognitive disorders. Currently, numerous cognitive and affective disorders are correlated with inappropriate noradrenergic neurotransmission [21]. These include Alzheimer's disease (AD), posttraumatic stress disorder (PTSD), depression, and attention deficit disorder. Although evidence for direct causal involvement of NA in the etiology of these disorders is lacking, alterations in the noradrenergic system can contribute to clinical symptoms. Processes regulating the release, reuptake, and signaling of NA therefore represent viable targets for pharmacological therapies. However, modifying the fine balance of neuromodulatory activity in the CNS is not without inherent risks. Increases or decreases in levels of NA can have detrimental effects on cognition. The following clinical disorders highlight memory problems associated with altered levels of NA in the brain.

7.1. Posttraumatic Stress Disorder (PTSD)

Patients with PTSD repetitively and involuntarily recall previous traumatic episodes in the form of potent daytime memories, nightmares, and flashbacks [215]. The neural and hormonal mechanisms responsible for this disorder are still speculative, but systems involved in emotional memory figure prominently.

Increased activity of the sympathetic nervous system and consequently, increased plasma levels of NA and adrenaline, are common in PTSD [216,217]. Levels of NA and adrenaline in cerebrospinal fluid are similarly augmented in PTSD patients compared to controls, and these levels correlate with the severity of symptoms [218]. Furthermore, administration of drugs that increase release of NA to veterans with PTSD elicits intrusive memories and flashbacks [219]. Pathologic increases in noradrenergic activity are therefore strongly implicated in the expression of PTSD.

As discussed earlier, NA is critical for retrieval of hippocampal memory and enhanced retention of emotional episodic memory. During a traumatic experience, it is likely that the noradrenergic neuromodulatory system is highly active, facilitating encoding and consolidation of memory for the trauma. Retrieval of this memory could induce stress and

further release of NA and adrenaline. In this manner, a positive feedback loop occurs, leading to over-consolidation of the memory for the traumatic experience and increased probability of its future retrieval [220,221]. Additionally, high levels of NA impair function of the prefrontal cortex [222]. The prefrontal cortex is subsequently unable to block the processing of inappropriate stimuli and responses, permitting the recall of traumatic, painful memories [215,223].

As such, pharmacological therapies targeting neuromodulatory systems are being investigated for the treatment of PTSD. One treatment for this disorder is administration of a selective serotonin reuptake inhibitor (SSRI). Although these drugs alter serotonergic neurmodulation, they can also substantially alter noradrenergic transmission [224]. Indeed, a double-blind randomized clinical trial shows that reboxetine (a selective noradrenaline reuptake inhibitor) and fluvoxamine (a SSRI) are equally efficacious in treating motor-vehicle accident-related PTSD [225]. The reciprocal interactions between these two neuromodulatory systems often complicate the pathophysiology of psychiatric disorders, but may offer alternative management options for difficult to treat conditions [225,226].

Clinical trials with drugs specifically targeting the noradrenergic system have also been pursued. The α2-adrenergic agonist clonidine suppresses NA release and decreases symptoms of hyperarousal, hypervigilance, sleep disruption, nightmares, and irritability in PTSD patients [227-229]. Furthermore, administration of the β-adrenergic receptor antagonist propranolol immediately after a traumatic experience may decrease the probability of subsequent PTSD symptoms [230].

The diverse symptoms and predisposing factors associated with PTSD suggest that this disorder involves numerous neuromodulatory and hormonal systems. Although NA potentially plays a prominent mechanistic role in PTSD, the contributions of other neuromodulatory systems and psychosocial factors cannot be ignored [231]. However, pharmacological manipulation of the noradrenergic system represents a promising therapy for this disorder (Fig. **5**).

7.2. Neurodegenerative Disorders

Alterations in neuromodulatory systems play a central role in the progression of Alzheimer's disease (AD), a prevalent neurodegenerative disorder [232]. AD is characterized by the persistent decline of memory, language skills, judgment, and attention. Although the etiology of AD is unknown, prominent neuropathology is observed in the hippocampus and other MTL structures [233].

Numerous neurotransmitter abnormalities are found in post-mortem AD brains. Specific deficiencies in the noradrenergic system are highly correlated with pathology and progression of illness in AD patients. Severe loss of noradrenergic neurons from the LC occurs in AD, and this loss more accurately reflects duration of illness than cell loss in other brain areas [234]. Furthermore, brain region-specific NA levels are decreased in AD patients relative to age-matched controls [235,236]. Noradrenergic deficiencies arising from loss of LC function are therefore hypothesized to be a critical component in the pathogenesis in AD.

Decreased noradrenergic activity is also implicated in the age-related decline of memory function. LC stimulation, direct interventricular infusions of NA, or application of α2-adrenergic receptor antagonists reduces memory deficits in aged animals for inhibitory avoidance and spatial memory tasks [237-239]. Increases in NA also augment memory in animals with insufficiencies of the cholinergic neuromodulatory system [237,240]. In fact, the selective noradrenaline reuptake inhibitor (SNRI) atomoxetine may facilitate memory and attention by increasing levels of acetylcholine in cortical brain regions [241]. The facilitatory effects of NA on memory and its interactions with other neuromodulatory systems suggest that NA may be an important target for pharmacological enhancement of cognitive function in AD.

However, little evidence connects the noradrenergic pathophysiology of AD to treatment options for patients. The equivocal results of studies examining the effects of noradrenaline on certain forms of memory in normal human subjects may contribute to this disconnection. Whereas evidence suggests that blocking central noradrenergic receptor activity with propranolol impairs working memory in normal human subjects, studies that increase noradrenaline levels with SNRIs generally show inconsistent effects on working memory [242]. It is also possible that pharmacological treatments may have different outcomes in normal human subjects compared to patients with neurodegenerative disorders. The α2-adrenergic receptor antagonist idazoxan enhances attention and episodic memory in patients with frontal type dementia, but is without effect on spatial recognition, memory, or sustained attention in normal volunteers [243,244]. Further investigation into the cognitive effects of these drugs is required to fully ascertain the outcome of enhancing NA in normal subjects and in those with neurodegenerative disorders such as AD.

Increased NA release and consequent blockade of α2-adrenergic receptors may also play neuroprotective roles in neurodegenerative disorders. For instance, signaling downstream of α1- and β-adrenergic receptors can up-regulate release of neurotrophic substances [245,246] and suppress pro-inflammatory gene expression in the brain [247]. NA is also crucial for proliferation of hippocampal granule cell progenitors, implicating this neuromodulator in neurogenesis [248]. These effects, among others, suggest that the noradrenergic neuromodulatory system may protect against, or aid recovery from, neural injuries and diseases.

Given the critical role of the noradrenergic neuromodulatory system in hippocampal synaptic plasticity and memory, the decreased NA activity observed in patients with AD could importantly contribute to cognitive impairments by impeding expression of some forms of synaptic plasticity. Decreased levels of NA could also impair neuroprotective processes that normally prevent chronic neuronal injury. As such, pharmacological agents that enhance levels of NA represent a viable target for clinical trials, and may address both the symptoms and progression of neurodegenerative disorders [232] (Fig. **5**).

8. CONCLUSIONS AND CAVEATS

Activation of neuromodulatory receptors in the CNS can alter cognition. The re-organization of network activity

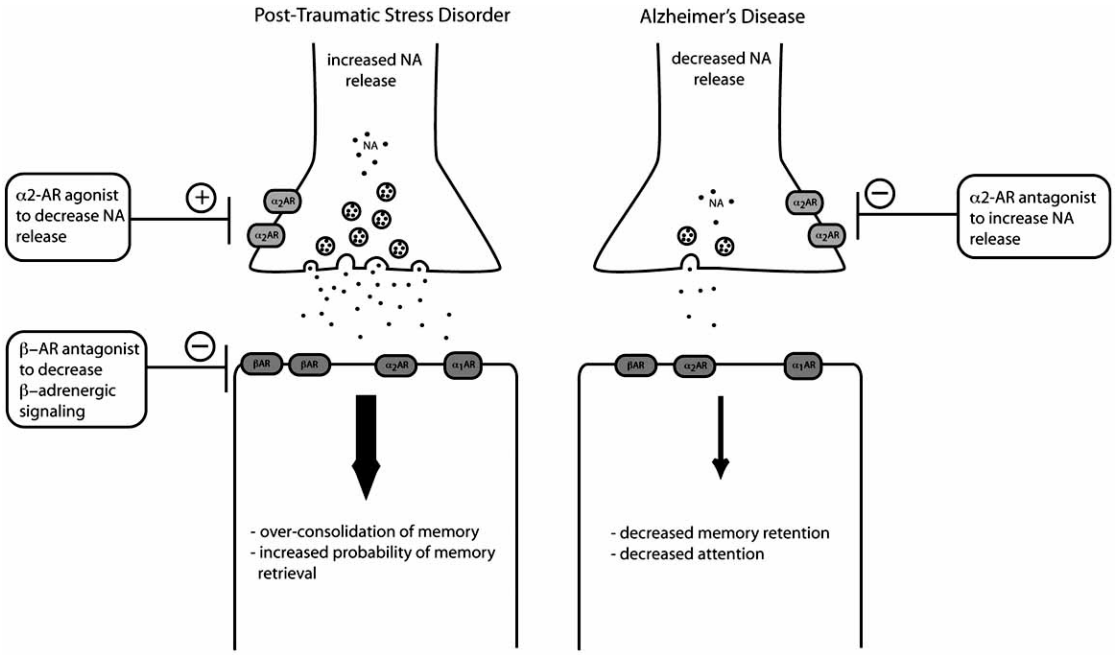

Fig. (5). A model of abnormal noradrenergic synaptic transmission in PTSD and AD showing cognitive outcomes and potential pharmacological treatments.

across multiple brain regions is necessary for rapid behavioural adaptation. This remodeling of functional circuitry could be more efficiently accomplished by coordinated release of neuromodulators. NA is postulated to play a crucial role in the processing of relevant environmental stimuli and the subsequent activity-dependent modification of behaviour.

Noraderenergic fibres innervating the hippocampus at least partially mediate the effects of NA on memory. Activation of noradrenergic receptors in this brain region has profound effects on synaptic plasticity, a key candidate cellular mechanism for memory. Furthermore, these receptors are involved in enhancements of hippocampus-dependent memory and emotional memory via interactions with the amygdala.

Because of the complexity of interactions between neuromodulation and network activity in different hippocampal subregions, pinpointing a specific mechanistic role for NA in memory is challenging. Firstly, the profile of receptors activated during endogenous release of NA is difficult to ascertain experimentally. This complicates *in vitro* studies that employ exogenous application of specific pharmacological agonists and antagonists. Cellular responses observed *in vitro* may not accurately mimic cellular responses elicited by endogenous NA release *in vivo*.

Hippocampal subregions also substantially differ in their neural responses to NA. Studies of plasticity in one subregion cannot reflect the processing capacities of the whole hippocampus. As information traverses the hippocampal trisynaptic circuit, NA could differentially affect computational properties of the individual subregions. More precise knowledge of circuit-level interactions in each subregion, and in the whole hippocampus, is required to understand the potential contributions of noradrenergic receptors to plasticity and memory at a systems level.

It is also important to carefully design studies when investigating the role of NA in memory. The use of genetic evidence to corroborate pharmacological studies is especially beneficial. Pharmacological probes should be selected with attention to their efficacy and selectivity as receptor agonists or antagonists. Furthermore, behavioural tasks commonly used to test declarative memory in laboratory animals can be optimized to address how NA affects memory acquisition, consolidation, and retrieval. It is also unknown whether noradrenergic activation in distinct brain regions facilitates memory by recruiting similar mechanisms. As such, studies addressing effects of NA on hippocampal memory may not be broadly applicable to forms of memory involving other brain regions.

Despite these constraints, ample evidence supports the hypothesis that NA crucially modulates both hippocampal synaptic plasticity and memory. This interaction may be particularly critical when considering disorders of memory with a noradrenergic component. The amalgamation of cellular, computational and behavioural approaches will enhance our understanding of how NA controls expression of synaptic plasticity and memory in the mammalian brain. This knowledge can then be used to improve existing therapies, and identify novel treatment strategies, for diseases of cognition and memory in humans.

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LIST OF ABBREVIATIONS

A	=	Adrenaline
AD	=	Alzheimer's disease
BDNF	=	Brain-derived neurotrophic factor
CAMKII	=	Calcium-calmodulin-dependent kinase
cAMP	=	Adenosine 3', 5'-cyclic monophosphate
CNS	=	Central nervous system
COMT	=	Catechol-O-methyl transferase
DA	=	Dopamine
DAG	=	Diacylglycerol
EPSP	=	Extracellular postsynaptic potential
ERK	=	Extracellular-signal regulated kinase
Glu	=	Glutamate
G-protein	=	Guanine nucleotide-binding regulatory protein
HFS	=	High-frequency stimulation
IP3	=	Inositol triphosphate
LC	=	Locus coeruleus
LFS	=	Low-frequency stimulation
LTD	=	Long-term depression
LTM	=	Long-term memory
LTP	=	Long-term potentiation
MAO	=	Monoamine oxidase
MTL	=	Medial temporal lobe
mTOR	=	Mammalian target of rapamycin
NA	=	Noradrenaline
NST	=	Nucleus of the solitary tract
NMDA	=	N-methyl-D-aspartate
PKA	=	cAMP-dependent protein kinase
PKC	=	Protein kinase C
PTSD	=	Posttraumatic stress disorder
SSRI	=	Selective serotonin reuptake inhibitor
STM	=	Short-term memory
VDCC	=	Voltage-dependent calcium channel

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