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Review

Cognitive enhancers: Focus on modulatory signaling influencing memory consolidation ☆

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ABSTRACT

Biological research has unraveled many of the molecular and cellular mechanisms involved in the formation of long-lasting memory, providing new opportunities for the development of cognitive-enhancing drugs. Studies of drug enhancement of cognition have benefited from the use of pharmacological treatments given after learning, allowing the investigation of mechanisms regulating the consolidation phase of memory. Modulatory systems influencing consolidation processes include stress hormones and several neurotransmitter and neuropeptide systems. Here, we review some of the findings on memory enhancement by drug administration in animal models, and discuss their implications for the development of cognitive enhancers.

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1. Introduction

The advancement in research exploring the biological mechanisms underlying learning and memory has opened many avenues for the discovery of pharmacological treatments for cognitive dysfunction associated with ageing and brain disorders. Most research on candidate cognitive-enhancing agents is based on animal models in which behavioral outcomes assumed to represent specific aspects of

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cognitive function are measured. Although the translation from preclinical to clinical research has important limitations (as discussed elsewhere, e.g., see Sarter, 2006), animal models have enabled the identification of selective molecular mechanisms that can be targeted by potential cognitive enhancers.

In this review, we address experimental strategies and molecular targets for the development of cognitive enhancers, focusing on the preclinical effects of selected agents that modulate memory consolidation. This article does not provide a complete survey of studies on potential cognitive enhancers; rather, it discusses selected experimental approaches, neurochemical systems, and agents to illustrate the wide range of mechanisms that can be targeted for the development of therapeutic approaches to treat memory dysfunction.

2. Experimental investigation of memory enhancement: exploring drug influences on different stages and types of memory

The first demonstration of drug enhancement of cognition was the finding by Lashley (1917) that strychnine could facilitate maze learning in rats (for a review, see McGaugh and Roozendaal, 2009). In the 1960s and 1970s, many studies started to show that administration of agents altering the function of neurotransmitters, including dopamine, norepinephrine, acetylcholine, and γ-aminobutyric acid (GABA), could produce memory enhancement in rodents. Importantly, McGaugh and colleagues showed in a series of studies that memory retention could be enhanced when agents were injected *after* behavioral training (McGaugh, 1966; 1973; McGaugh and Petrinovich, 1959; McGaugh and Roozendaal, 2009). The introduction of such *posttraining* drug injections contributed a powerful approach for the experimental investigation of memory formation. When an animal is given a chemical agent before being trained in a behavioral task, or prior to memory retention testing, resulting alterations in behavioral performance might involve changes in aspects of brain function other than memory, for instance sensorimotor function, motivation, or anxiety. This can confound the interpretation of experimental findings as alterations in memory processing. Drug administration after training, on the other hand, enables the investigation of memory consolidation without affecting other aspects of behavior, provided that the drug does not produce long-lasting detrimental effects (McGaugh, 1989; McGaugh and Roozendaal, 2009; Roesler and McGaugh, 2010) (Fig. 1).

Evidence from studies describing the memory-modulating effects of drugs given after versus before the behavioral training or prior to the memory testing also highlights the importance of taking into account that neuromodulatory agents can produce different effects on distinct phases of memory, i.e. acquisition (or learning); consolidation; long-term persistence; reconsolidation; and expression (or retrieval). For instance, glucocorticoids can enhance consolidation but impair retrieval of memories associated with emotional content (de Quervain et al., 1998). Recent evidence indicates that long-term stabilization and persistence of memory after initial consolidation requires specific molecular mechanisms (Bekinschtein et al., 2007; Eckel-Mahan et al., 2008).

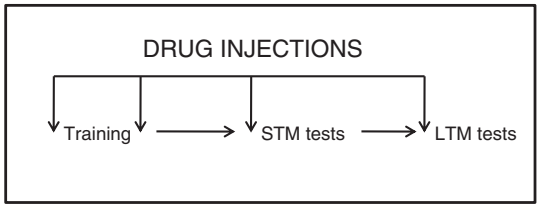

Fig. 1. Drug manipulation of different phases and types of memory. Animals given training in memory tasks can be tested for retention of short-term memory (STM) or long-term memory (LTM). Drug treatments given before training can affect both learning (memory acquisition) and memory consolidation. The use of posttraining drug injections allows the investigation of modulatory effects that specifically influence consolidation. Injections given before memory testing are used to investigate drug effects on the expression (retrieval) of STM or LTM.

Another critical factor for the experimental enhancement of memory is the specific type of memory being investigated. It is well established that short- and long-lasting memories show critical differences in their neural substrates. Thus, formation of long-, but not short-term memory, is impaired by agents that inhibit protein synthesis (Alberini, 2008; Davis and Squire, 1984), and agents acting on several neurochemical systems can affect short- but not long-term memory, indicating that these two forms of memory are processed in parallel and depend on different molecular substrates (Izquierdo et al., 1998; 1999). Moreover, the formation of memory for tasks involving different types of information (e.g., conditioning to aversive or rewarding stimuli, spatial location, multimodal contextual information, recognition of discrete objects, and motor responses) shows marked differences in their reliance on specific brain systems and modulation by neurotransmitters and hormones (Milner et al., 1998; Roesler and McGaugh, 2010).

The fact that each of the multiple types of memory is a complex process, involving several stages differentially regulated by neurochemical pathways, adds to the challenge of developing clinically efficacious and safe cognitive enhancers. An ideal cognitive enhancer should stimulate one's ability, which is often disrupted in dementia and psychiatric disorders, to learn and retain memories associated with a range of types of information, including contextual cues, spatial location, and object recognition; at the same time, it should not exacerbate memories that might become pathological, such as those of previous traumatic events. Moreover, a useful cognitive enhancer should be able to facilitate different stages of memory formation and expression, or at least to enhance one stage without disrupting others. Finally, it should not produce undesirable effects on parameters such as sensorial perception, anxiety, attention, or sleep. In summary, the effects of cognitive enhancers should be specific enough to promote beneficial cognition improvement without potentiating the formation and expression of unwanted and unnecessary memories or impairing other aspects of brain function.

3. Molecular basis of memory formation: identifying targets for cognitive enhancement

Extensive research over the past decades has focused on investigating the molecular mechanisms underlying synaptic modifications triggered by learning that enable the formation and long-term storage of memories. This field of investigation has greatly benefited from the tools and conceptual framework of molecular biology, which enabled researchers to think of cognitive processes in terms of cellular signaling events. The introduction of genetic engineering approaches to memory research in mice (transgenic and knockout techniques, including temporally restricted and spatially localized modifications) provided new tools allowing the identification of molecular targets for cognitive enhancement, based on the consequences on memory of genetic disruption or stimulation of discrete molecular mechanisms in whole animals or selected neuronal populations (Silva, 2003; Tonegawa et al., 2003). Also, the characterization and use of non-mammalian, invertebrate model organisms in memory research (e.g., the fruit fly *Drosophila* and the sea snail *Aplysia*) have progressively increased in amount and relevance, on the basis that simple forms of learning and their underlying molecular mechanisms are highly conserved evolutionary phenomena (Dubnau and Tully, 1998; Kandel, 2001. Margulies et al., 2005). Pharmacological and genetic manipulations in vertebrate or invertebrate animal models have thus played a complementary role in unraveling the biological basis of memory processing and ultimately identifying targets for cognitive enhancement

(Kandel, 2001; Lee and Silva, 2009; McGaugh and Izquierdo, 2000; Silva, 2003; Tonegawa et al., 2003).

The demonstration by Bliss and Lomo (1973) of the phenomenon of long-term potentiation (LTP), a persistent increase in synaptic response produced by high-frequency stimulation, provided the first direct experimental evidence that synaptic plasticity might be the basis of memory formation. Subsequent studies showed that LTP induction in the hippocampus was blocked by antagonism of the *N*-methyl-D-aspartate (NMDA) type of glutamate receptor, which is associated with a channel permeable to calcium and sodium cations. Morris and colleagues (1986) demonstrated that intracerebral administration of an NMDA receptor antagonist impaired learning of a spatial memory task, indicating that NMDA receptors are critical for both LTP and memory. Currently, extensive evidence indicates that several types of learning trigger activation of NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and metabotropic (mGluR) glutamate receptors, initiating the sequence of cellular signaling events that mediate synaptic plasticity and learning (Nakazawa et al., 2004; Riedel et al., 2003). Protein kinase signaling cascades are activated downstream of glutamate receptors, including the calcium-calmodulin-dependent protein kinase II (CaMKII), phospholipase C (PLC)/protein kinase C (PKC), cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/cAMP response element binding protein (CREB), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated protein kinase (ERK), and phosphatidylinositol 3-kinase (PI3K) pathways. This results in de novo protein synthesis and expression of specific immediate-early genes including c-fos, Arc, and zif268, ultimately leading to alterations in gene expression, structural synaptic reinforcement, and growth of new synaptic connections (Alberini, 2009; Carew, 1996; Izquierdo and Medina, 1997; Kandel, 2001; McGaugh, 2000; Roesler and McGaugh, 2010). Long-term persistence of memory after initial consolidation involves specific molecular mechanisms, including a delayed stabilization phase dependent on brain-derived neurotrophic factor (BDNF) and protein synthesis (Bekinschtein et al., 2007), as well as activation of the cAMP/PKA/CREB and MAPK pathways in the hippocampus during the circadian cycle (Eckel-Mahan et al., 2008). Importantly, long-term maintenance of both memory and LTP requires persistent phosphorylation by the atypical protein kinase C isoform, protein kinase Mzeta (PKMz) (Pastalkova et al., 2006; Serrano et al., 2008), through a mechanism involving PKMz regulation of AMPA receptor density in the postsynaptic membrane (Migues et al., 2010). This evidence, together with electrophysiological experiments showing that learning and memory consolidation produce LTP-like changes in hippocampal synapses (Gruart et al., 2006; Whitlock et al., 2006) has consistently supported the view that memory formation relies on LTP or a process very similar to LTP.

The set of signaling events described above, considered to be at the core of synaptic modifications underlying memory formation provide a range of molecular targets for cognitive enhancement. To illustrate this, below we will briefly discuss selected cognitive enhancers that act at some of the molecular events proposed to mediate synaptic plasticity. At least some of these agents are capable of enhancing memory by specifically modulating consolidation.

3.1. Cognitive enhancers acting on glutamate receptors

The critical role of glutamate receptors in triggering most types of LTP and learning makes them obvious targets for cognitive enhancement. This is supported by the findings that genetic overexpression of the NR2B NMDA receptor subunit in the mouse brain enhanced LTP and performance in several memory tasks (Tang et al., 1999). In fact, drugs that stimulate glutamate receptors have been investigated in both animal models and clinical studies. For example, d-cycloserine, which stimulates the NMDA receptor by acting as a partial agonist at its glycine binding site, enhances learning and rescues age-related deficits in LTP and memory in rats (Baxter et al., 1994; Billard and Rouaud, 2007), facilitates learning and memory consolidation in healthy humans (Kalisch et al., 2009; Onur et al., 2010), and has been evaluated in clinical trials in Alzheimer's disease patients (Laake and Oeksengaard, 2002; Schwartz et al., 1996). However, there are several challenges for the development of clinically acceptable NMDA receptor-stimulating agents. Excessive stimulation of NMDA receptors mediates neuronal death by the process known as excitotoxicity (Lipton and Rosenberg, 1994). In addition, NMDA receptor involvement in memory processing might be rather complex. For instance, NMDA receptors may be required for acquiring memories of novel types of information, but not for memories for which some components have been previously learned (Bannerman et al., 1995; Roesler et al., 1998; 2003b). Memantine is a noncompetitive NMDA receptor antagonist introduced for the treatment of Alzheimer's disease (Lipton, 2005; Lipton and Chen, 2005; McShane et al., 2006). Because the disease progression might involve neuronal damage partially mediated by glutamate excitotoxicity, memantine can display antioxidant and neuroprotective effects, resulting in beneficial effects on cognitive function. In addition, memantine can rescue memory deficits associated with aging possibly by reducing brain oxidative stress (Pietá Dias et al., 2007). Thus, the cognitive improvement produced by memantine is proposed to be related to its neuroprotective actions after chronic treatments rather than an influence on mechanisms underlying memory processing per se (Butterfield and Pocernich, 2003; Lipton, 2005). In fact, memantine can impair memory by blocking NMDA receptor activation (Creeley et al., 2006). However, some studies have shown that acute administration of memantine can rescue memory deficits in experimental models of amnesia (Barber and Haggarty, 2010, Yuede et al., 2007). Other agents developed as potential cognitive enhancers that act by stimulating glutamatergic transmission include ampakines, which positively modulate AMPA receptors (Lynch, 1998; 2006; Lynch and Gall, 2006; Lynch et al., 2008).

3.2. Drug enhancement of memory by stimulation of the cAMP/PKA/CREB pathway

The cAMP/PKA/CREB pathway represents one of the main targets for the development of cognitive enhancers for the treatment of patients with memory dysfunction (Arnsten et al., 2005; Scott et al., 2002; Tully et al., 2003). The central role of this pathway in memory formation was first suggested by studies in *Aplysia* (Dash et al., 1990) and *Drosophila* (Tully, 1997). Subsequent studies in rodents showed a critical role for PKA and CREB in consolidation of long-term memory (Abel et al., 1997; Guzowski and McGaugh, 1997). Increases in cellular cAMP levels lead to activation of PKA, which recruits MAPK and translocates to the nucleus, where it activates the transcription factor CREB, resulting in altered expression of target genes. Drugs that enhance cAMP/PKA signaling can improve memory by directly modulating consolidation processing: these agents enhance memory when infused at specific time points after training into different brain areas in rats (Bevilaqua et al., 1997; Roesler et al., 2002).

Agents that stimulate cAMP/PKA/CREB signaling include inhibitors of the phosphodiesterase type 4 (PDE4) isoform, an enzyme that catalyzes hydrolysis of cAMP. For example, rolipram, a specific PDE4 inhibitor, has been shown to enhance both hippocampal long-term potentiation (LTP) and memory in mice (Barad et al., 1998). In addition, rolipram ameliorates deficits in LTP and memory in a range of pharmacological and genetic rodent models of amnesia (Alarcón et al., 2004; Bach et al., 1999; Gong et al., 2004; Zhang et al., 2004). We have recently shown that a single posttraining injection of rolipram ameliorates deficits in object recognition memory associated with aging or iron overload-induced amnesia in rats, indicating that PDE4 inhibitors are able to rescue cognition deficits by specifically modulating memory consolidation (de Lima et al., 2008) (Fig. 2).

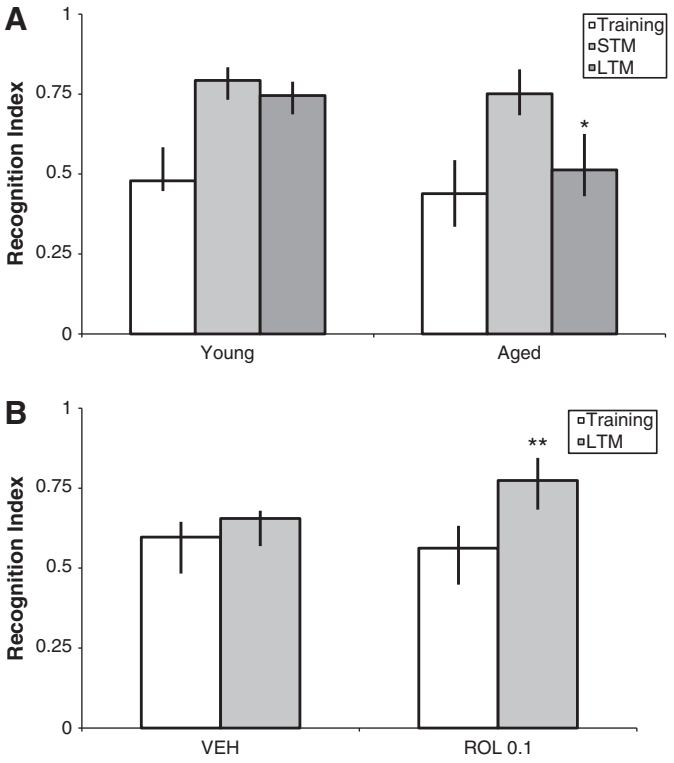

Fig. 2. PDE4 inhibitors can produce memory enhancement by specifically modulating consolidation. A. Aged rats show impaired recognition memory. Young (3 months-old) and aged (24 months-old) male rats were trained in a novel object recognition task and tested for retention at 1.5 (STM) and 24 h (LTM) after training. Data are median (interquartile ranges) exploratory preference during the training, STM and LTM retention test trials; $^{*}P<0.05$ compared to young male rats. B. A single posttraining systemic injection of the PDE4 inhibitor rolipram (ROL) rescues the age-related deficit in LTM. Twenty-three month-old male rats were given an intraperitoneal (i.p.) injection of VEH or ROL (0.1 mg/kg) immediately after training in novel object recognition. Memory retention was tested 24 h after training. Data are median (interquartile ranges) exploratory preference during the training and 24-h LTM retention test trials; $^{*}P<0.05$ compared to VEH-treated rats. Reproduced from de Lima et al., 2008.

3.3. Drugs acting on epigenetic mechanisms

As discussed above, most of the research on cognitive enhancement by manipulation of the molecular mechanisms mediating memory formation has focused on drugs targeting neuronal receptors or their downstream protein kinase pathways. More recently, an increasing number of studies have examined memory alterations induced by agents that act on epigenetic mechanisms regulating gene expression, for example, chromatin remodeling, histone modification, and DNA methylation (Alarcón et al., 2004; Guan et al., 2002; Korzus et al., 2004; Levenson et al., 2004). Histone deacetylase (HDAC) inhibitors (HDACi) represent the main class of experimental cognitive enhancers targeting epigenetic mechanisms currently under investigation. Histone acetylation alters chromatin structure, affecting transcriptional regulation within the chromatin to increase accessibility for transcriptional regulatory proteins. It has recently been shown that alterations in histone acetylation in the mouse brain are associated with age-dependent memory impairment (Peleg et al., 2010). Several recent studies show that systemic or intracerebral administration of HDACis (including sodium butyrate, trichostatin A, and valproic acid) to rats and mice enhance learning of several tasks and rescues experimental amnesia (Bredy and Barad, 2008; Fischer et al., 2007; Korzus et al., 2004; Levenson et al., 2004; Stefanko et al., 2009; Vecsey et al., 2007). HDACis can regulate consolidation to enhance memory, since they produce effects when given posttraining (Federman et al., 2009; Roozendaal et al., 2010), and increased histone acetylation might be a molecular feature associated with consolidation of stronger memories (Federman et al., 2009). The memory-enhancing effects of HDACis might be mediated primarily by activation of genes regulated by the CREB:CREB-binding protein (CBP) transcriptional complex (Vecsey et al., 2007).

4. Memory enhancement by pharmacological manipulation of modulatory influences on consolidation

4.1. Modulatory signaling influencing memory consolidation

Learning experiences trigger synaptic modifications, likely mediated by the sequence of molecular and biochemical mechanisms described above, resulting in formation and long-term storage of new memories. However, the strength of the memory trace being formed can be regulated after learning and during consolidation. The concept of "memory modulation" is often used to refer to the influence of drugs and hormones, particularly endogenous hormone systems activated by emotionally arousing learning experiences, on the strength of the memory undergoing consolidation (McGaugh, 2000; McGaugh and Roozendaal, 2009). The concept of modulation of brain function is also broadly used to describe the actions of neurotransmitters including dopamine, noradrenaline, acetylcholine, serotonin, and neuropeptides ("modulatory" neurotransmitter systems), which can regulate neuronal function by altering the activity of intracellular signaling pathways downstream of receptor activation. In the context of memory research, the term "modulation" can thus serve to describe the alterations in memory strength resulting from the actions of hormonal and neurotransmitter systems (e.g., adrenaline, glucocorticoids, noradrenaline, dopamine, and neuropeptides), as well as of drugs acting on these endogenous systems, upon consolidation.

One might think of biochemical systems and events involved in long-term memory formation as being either "core" mechanisms (or key molecular "switches") triggered by learning and critical for synaptic modifications (e.g., glutamate receptor activation, CREB activation, and protein synthesis), or "modulatory" mechanisms, which are not critical for memory formation itself but can regulate its strength (e.g., release of stress hormones, activation of noradrenergic, and dopaminergic neuronal pathways). However, the dissociation between "core" and "modulatory" mechanisms in memory processing is less clear at the cellular level, since the transduction of different extracellular signals (neurotransmitters, neuropeptides, and neurotrophins) share most of the same intracellular signaling pathways (protein kinases, transcription factors, and gene expression). For instance, CREB activation (proposed as a key or "core" switch for consolidation of long-term memory) can result from the actions of a range of different "modulatory" signals, including norepinephrine, dopamine, serotonin, and neuropeptides. Thus, memory formation at the molecular and cellular level results from the integration of a range of different extracellular signals into a complex network of intracellular biochemical events that converge to structural synaptic modifications, without clear distinction between "core" and "modulatory" signals.

Within the context of this review, we refer to cognitive-enhancing agents acting on "modulatory systems", or "modulatory signaling", as those that can influence memory consolidation by acting on hormone systems including adrenaline and glucocorticoids, or neurotransmitter systems including noradrenaline, dopamine, acetylcholine, serotonin, GABA, and neuropeptides. The effects of agents that enhance memory by influencing memory consolidation share some common properties. First, the effects typically show an inverted U-pattern of dose response in which memory enhancement is produced at a narrow dose range. This represents a significant challenge for the development of clinically useful cognitive enhancers targeting modulatory systems. Second, the basolateral nucleus of the amygdala (BLA) is a brain area critical in enabling memory enhancement by drugs and hormones. Lesions or pharmacological inhibition of the BLA can block the memory

enhancement produced by a wide variety of agents acting on modulatory systems without disrupting memory formation per se, and the effects of many modulating drugs are similar when administered systemically and infused specifically into the BLA (reviewed in McGaugh, 2002; 2004; McGaugh et al., 1996). Thus, research focusing on the development of cognitive enhancers based on memory modulation should take into consideration the critical role of neurochemical systems within the BLA in mediating memory drug enhancement of memory. Selected illustrative examples of memory-enhancing drugs acting on modulatory systems are discussed below.

4.2. Drugs acting on adrenergic/noradrenergic receptors

Extensive evidence indicates that endogenous hormones released after learning experiences, i.e. adrenaline and cortisol (corticosterone in the rat) can enhance consolidation of emotional memories (reviewed in McGaugh and Roozendaal, 2002; 2009). Early studies in the 1970s were the first to show that adrenaline injected after training enhanced memory retention in rats (Gold et al., 1977; Gold and van Buskirk, 1975). These early findings have been replicated by an extensive number of studies. The effects of adrenaline on memory are probably mediated by activation of beta-adrenergic receptors on the ascending vagus nerve that projects to the nucleus of the solitary tract, resulting in activation of the noradrenergic system in the forebrain. Noradrenergic activation within the BLA is critical in mediating the memory-enhancing effects of systemically administered adrenaline (Liang et al., 1986). Infusion of noradrenaline into the BLA or other brain areas including the dorsal hippocampus can produce memory enhancing effects comparable to those induced by systemic injections of adrenaline (Bevilaqua et al., 1997; LaLumiere et al., 2003). We have recently shown that posttraining administration of adrenaline enhances memory for object recognition, a task considered to involve lower levels of motivation and arousal compared to aversive conditioned tasks usually used in the investigation of the role of the adrenergic system on memory. Importantly, rats given adrenaline showed sustained memory retention across consecutive daily memory retention tests, whereas memory in control rats decreased and was significantly impaired compared to adrenaline-treated rats 96 h after learning (Dornelles et al., 2007). These findings indicate that adrenaline can enhance memory consolidation for different types of learning associated with distinct levels of arousal, and that adrenaline can enhance cognition by producing an increase in the persistence of memory over time.

In addition to adrenaline and noradrenaline, drugs acting at specific subtypes of noradrenergic receptors can enhance memory by modulating consolidation. For example, posttraining intracerebral infusion of the alpha-2 adrenoceptor agonist clonidine was shown to enhance memory for aversive training in chicks (Gibbs and Summers, 2003). Infusion of the beta-2 adrenoceptor agonist clenbuterol, the alpha-2 adrenoceptor antagonist idazoxan, or the non-selective alpha-adrenoceptor agonist phenylephrine combined with the alpha-2 adrenoceptor antagonist yohimbine, into the BLA after training enhanced memory for inhibitory avoidance conditioning in rats (Ferry et al., 1999; Ferry and McGaugh, 1999; 2008). Alfa-2 adrenoceptor antagonists given before training were shown to act synergistically with an acetylcholinesterase inhibitor to enhance memory for inhibitory avoidance in rats (Camacho et al., 1996).

4.3. Drugs acting on glucocorticoid receptors

Glucocorticoid hormones released peripherally readily enter the brain and act at neuronal glucocorticoid receptors in several brain regions including the dorsal hippocampus and the BLA. Glucocorticoid receptor agonists, such as the corticosteroid dexamethasone, enhance memory in rats when given systemically after training (Quevedo et al., 2002; Quirarte et al., 1997; Roesler et al., 1999; Roozendaal and McGaugh, 1996). Memory enhancement can be also produced by infusions of the glucocorticoid receptor type II agonist RU 28362 into the BLA or dorsal hippocampus after training (Roozendaal and McGaugh, 1997a; 1997b; Roozendaal et al., 1999). Memory enhancement by glucocorticoid receptor agonists depends on noradrenergic signaling and the cAMP/PKA pathway within the BLA (Quirarte et al., 1997; Roozendaal et al., 2002). Importantly, a recent study indicated that increased histone acetylation plays a role in memory enhancement induced by glucocorticoids, suggesting a role for epigenetic modifications in mediating the modulatory influences of hormones on memory consolidation (Roozendaal et al., 2010). The role of glucocorticoids in regulating memory consolidation has been reviewed in detail elsewhere (Roozendaal, 2000).

The development of cognitive enhancers based on stress hormone systems would pose several major challenges. First, pharmacological stimulation of glucocorticoid or adrenergic receptors would likely increase unwanted systemic responses associated with stress and cortisol release (e.g., metabolic alterations) and (in the case of adrenergic agonists) sympathetic activation (e.g., increases in heart rate and blood pressure), potentially producing side effects unacceptable for clinically safe cognitive enhancers. Second, as noted above, stress hormone systems enhance consolidation but impair memory retrieval (de Quervain et al., 1998; Roozendaal, 2002). The development of more specific agents that can produce cognitive enhancement without significantly affecting peripheral responses or impairing effects on memory expression is necessary for glucocorticoid receptors to represent more promising targets for the development of cognitive-enhancing treatments.

4.4. Drugs acting on cholinergic transmission

The acetylcholinesterase inhibitors (AChEi) donepezil, rivastigmine, and galantamine are established in the treatment of Alzheimer's disease. AChEis can enhance memory when injected after training (Santucci et al., 1989; Stratton and Petrinovich, 1963). Memory consolidation can also be enhanced by systemic or intra-cerebral administration of muscarinic cholinergic receptors in rats and mice (LaLumiere and McGaugh, 2005; Pavone et al., 1993; for a review, see Power et al., 2003). Acute posttraining systemic administration of galantamine or the muscarinic receptor agonist oxotremorine rescued memory impairment induced by neonatal iron overload in rats (Perez et al., 2010), a model of memory dysfunction associated with Alzheimer's and Parkinson's disease (Fernandez et al., 2010; Schröder et al., 2001).

Nicotine has been consistently shown to display cognitive-enhancing effects. It enhances attention and memory in both animals and humans, and other agonists at nicotinic cholinergic receptors have been developed and tested as potential cognitive enhancers (Warburton, 1992). Animal studies using posttraining injections of nicotine or other agonists have indicated that nicotinic receptors positively modulate consolidation (Barros et al., 2005; Borta and Schwarting, 2005; Gould and Lommock, 2003; Kenney et al., 2010; Puma et al., 1999).

4.5. Drugs acting on dopaminergic transmission

The memory enhancing effects of amphetamine, which acts partially by stimulating dopaminergic transmission, have been known for decades. More recently, studies have focused on drugs that act at specific types of dopamine receptors (Mehta and Riedel, 2006). Dopamine D1/D5 receptors are coupled to activation of the cAMP/PKA/CREB pathway. Thus, D1/D5 receptor agonists represent an effective pharmacological strategy to activate cAMP signaling in order to produce enhancements in synaptic plasticity and memory. In fact, the maintenance of some forms of hippocampal LTP requires D1/D5 receptors (Navakkode et al., 2007), and infusion of the D1/D5 receptor agonist SKF 38393 into the hippocampus or cortical areas at different

time intervals after training enhances memory retention in rats (Ardenghi et al., 1997. Bevilaqua et al., 1997). SKF 38393 also rescues age-related deficits in LTP and hippocampal memory in mice by activating the CREB pathway (Bach et al., 1999). Dopamine enhances memory when infused posttraining into the BLA through a mechanism dependent on both D1 and D2 receptors (LaLumiere et al., 2004). Memory enhancement has also been described after injections of D2 and D3 receptor antagonists (Setlow and McGaugh, 2000; Sigala et al., 1997). We have recently found that systemic posttraining administration of SKF 38393, but not of the D2 receptor agonist, quinpirole, induced an enhancement of object recognition memory in rats. In addition, the non-selective dopamine receptor agonist apomorphine enhanced recognition memory in a condition in which D2 dopamine receptors were blocked by raclopride. These findings indicate that posttraining pharmacological activation of D1, but not D2 receptors, can enhance recognition memory (de Lima et al., 2011). Agents developed in recent years as cognitive enhancers that target dopamine receptors include the D1/D5 receptor agonist dihydrexidine (George et al., 2007; Steele et al., 1996) and the D4 receptor agonist A-412997 (Browman et al., 2005; Woolley et al., 2008).

4.6. Drugs acting on neuropeptide receptors

Neuropeptides constitute a major class of signaling molecules within the brain. Many neuropeptide systems have been shown to regulate learning and memory, in most cases by facilitating encoding, consolidation, or retrieval. Neuropeptides influencing memory include opioids, vasopressin, cholecystokinin (CCK), oxytocin, neuropeptide Y, neuropeptide S, galanin, adrenocorticotropin (ACTH), corticotrophin-releasing hormone (CRH), somatostatin, substance P, vasoactive intestinal peptide (VIP), and bombesin-like peptides. Many recombinant human and animal neuropeptides, as well as synthetic peptides that act as agonists or antagonists at neuropeptide receptors, are currently available as research tools or experimental drugs for studies of cognitive enhancement. In the context of drug development, the use of peptidergic molecules as cognitive enhancers is often hampered by the need to use subcutaneous or intravenous routes of administration and poor permeability through the blood-brain barrier. In some cases, these limitations are being circumvented by the development of intranasal formulations that allow efficient delivery of peptidergic molecules to the brain (Fehm et al., 2000). A general view of the role of neuropeptides in memory modulation has been presented in several reviews (Bennett et al., 1997; de Wied, 1997; Engelmann et al., 1996; Feany, 1996; Fehm et al., 2000; Gülpinar and Yegen, 2004; Huston and Hasenöhrl, 1995; Koob et al., 1989; Ogren et al., 2010). Here we will focus on the gastrin-releasing peptide (GRP) as an illustrative example of neuropeptide involved in modulating memory that can be targeted for cognitive enhancement.

GRP, the mammalian analog of the amphibian peptide bombesin, is a neuropeptide belonging to the family of bombesin-like peptides. Both GRP and bombesin act primarily by activating G-protein coupled GPR receptors (GRPR and BB2 receptors) on the cell membrane. In the mammalian brain, the GRPR is selectively expressed on post-synaptic neuronal membranes and particularly enriched in brain areas including the dorsal hippocampus and BLA, and GRP is likely co-released with glutamate from excitatory neurons (Moody and Merali, 2004; Roesler et al., 2006a). GRPR blockade by posttraining systemic, intrahippocampal, or intra-BLA administration of the GRPR antagonist RC-3095 impairs memory formation in rats (Roesler et al., 2003a; 2004a; 2004b; Venturella et al., 2005). Conversely, GRPR activation in the hippocampus by posttraining infusions of bombesin enhanced retention of memory for inhibitory avoidance training (Roesler et al., 2006b). Memory enhancement by intrahippocampal bombesin was prevented by RC-3095 or inhibitors of PKA, MAPK/ERK, PKC, and PI3K, and potentiated by agents stimulating cAMP/PKA/CREB signaling (Roesler et al., 2006b; 2009). Importantly, intrahippocampal infusion of bombesin rescued inhibitory avoidance memory in a model of cognitive impairment induced by infusion of a small dose of beta-amyloid peptide (25–35) into the rat CA1 area of the hippocampus (Roesler et al., 2006b).

The effects of drugs acting on the GRPR on memory consolidation show many typical features of memory enhancement by modulatory systems. First, the effect shows an inverted U pattern of dose response where intermediate doses of bombesin enhance memory, whereas higher doses are memory-impairing (Roesler et al., 2006b); conversely, lower doses of RC-3095 impair, and high doses enhance, memory (Dantas et al., 2006). Second, memory modulation by GRPR ligands critically depends on the BLA; functional inactivation of the BLA prevents memory modulation by posttraining systemic injection of RC-3095 (Roesler et al., 2004b). Finally, GRPR signaling is coupled

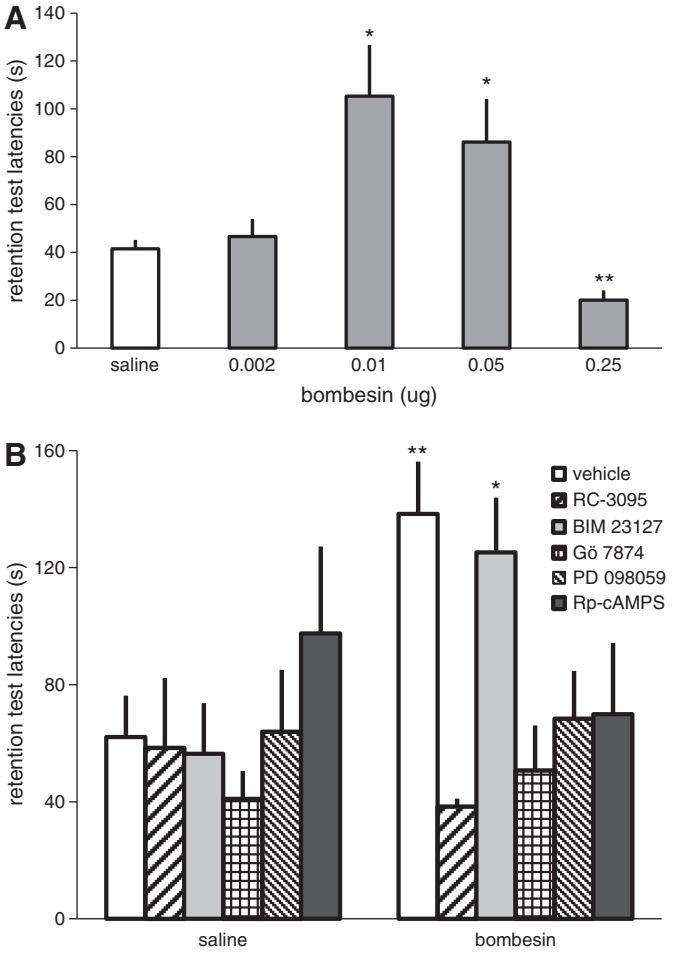

Fig. 3. Memory enhancement by bombesin illustrates the modulatory effects of neuropeptide systems on consolidation. A. Adult male rats were trained in an inhibitory avoidance task and tested for retention 24 h after training. Recombinant bombesin (0.002, 0.01, 0.05, or 0.25 μg) or saline was infused bilaterally into the CA1 area of the dorsal hippocampus immediately after training. Bombesin-induced memory enhancement is observed at intermediate doses, whereas a higher dose impairs memory. Data are mean ± SEM 24-h retention step-down latencies (s); $^{*}P<0.05$ and $^{**}P<0.01$ compared to the saline-treated group. B. GRPR activation and protein kinase signaling pathways mediate the memory enhancement produced by posttraining infusion of bombesin into the hippocampus. Rats were given bilateral intrahippocampal infusions of the GRPR antagonist RC-3095 (0.2 μg), the neuromedin B receptor (NMBR) antagonist BIM 23127 (0.1 μg), the PKC inhibitor Gö 7874 (0.5 pg), the MAPK kinase inhibitor PD098059 (5.0 ng), the PKA inhibitor Rp-cAMPs (0.02 μg), or vehicle 10 min before inhibitory avoidance training, and bombesin at a memory-enhancing dose (0.01 μg in 0.5 μl) or saline immediately after training. The GRPR antagonist and inhibitors of the PKC, ERK/MAPK, and PKA pathways at the doses used did not block memory formation, but prevented the bombesin-induced enhancement. Data are mean ± SEM 24-h retention step-down latencies (s); $^{*}P<0.05$ and $^{**}P<0.01$ compared to the control group treated with vehicle and saline. Reproduced from Roesler et al., 2006b.

to activation of intracellular protein kinase pathways that are crucially involved in synaptic plasticity and memory consolidation (Fig. 3). It is worth pointing out that GRPR blockade by RC-3095 given during the neonatal period produced long-lasting impairments in long-term memory for both object recognition and inhibitory avoidance, suggesting a role for the GRPR in the development of normal cognitive function (Presti-Torres et al., 2007). Based on these findings, we have put forward the GRPR as a target in memory dysfunction and other types of brain disorders (Presti-Torres et al., 2007; Roesler et al., 2006a).

4.7. Other cognitive enhancers acting on modulatory systems

Several other modulatory systems, in addition to the ones reviewed above, play an important role in regulating memory formation and may serve as targets for the development of cognitive enhancers. Drugs under investigation include agents targeting receptors and transporters for GABA, cannabinoids, serotonin, and adenosine, among others.

5. Conclusion

Memory dysfunction associated with aging or neurodegenerative and psychiatric disorders represents an increasing unmet medical need. The remarkable advances in our understanding of the molecular basis of memory formation in the past few decades have opened an avenue for the development of memory-enhancing therapies targeted at selective neuronal targets. In preclinical models, memory can be enhanced by a wide variety of pharmacological agents targeting signaling mechanisms that regulate memory consolidation. These modulatory systems include stress hormones, neurotransmitters including norepinephrine, acetylcholine, and dopamine, and neuropeptides. At the cellular level, these modulatory signals converge to influence intracellular signaling pathways, gene expression, and protein synthesis, resulting in structural synaptic alterations. However, because of the high complexity of memory processing and dysfunction in humans, experimental cognitive enhancement has not yet translated into successful clinical treatments. As discussed above, drugs can produce very different effects on distinct phases and types of memory, and relatively subtle aspects (e.g., novelty content, contextual information, and stress levels) associated with each particular memory can be critical factors in determining drug effects. This makes it very difficult to develop cognitive enhancers that have clinical usefulness as general memory stimulators, particularly if such proposed treatments target neuromodulatory signaling. These caveats and the limitations of preclinical studies for clinical applications no doubt will be addressed by neurobiological research and, hopefully give rise to new therapeutic opportunities.

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