CHAPTER 17

Enhancement of Learning and Memory Performance: Modality-Specific Mechanisms of Action

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> Many of us are anxious to find ways to improve our memories; none of us have to deal with the problem of how to forget. In S's case, however, precisely the reverse was true. The big question for him, and the most troublesome, was how he could learn to forget.
>
> From Luria, 1968, p. 67.

I. INTRODUCTION

The first edition of *Neurobiology of Learning and Memory* described the beneficial impact in several animal species of environmental enrichment and administration of mnemonic drugs on subsequent performance of a variety of learning and memory-intensive tasks. More recently, a great deal of attention has been focused on drug, nutriceutical, and lifestyle interventions capable of enhancing learning and memory capacity (McDaniel et al., 2003; Nyberg et al., 2003; Barch, 2004). At the present time, a concerted effort is under way to commercialize these basic neuroscientific discoveries (Marshal, 2004). One overarching research goal that has been articulated for the future is to couple the

Neurobiology of Learning and Memory, Second Edition

explanations of learning and memory processes at the systems and cellular levels of analysis (Weeber and Sweatt, 2002; Morris et al., 2003; Dash et al., 2004). This chapter attempts to rise to this challenge by employing cognitive, neuroanatomical, physiological, and molecular terminology to characterize several nervous system functions that are thought to be capable of enhancing learning and memory.

The main organizing theme for the chapter is represented by three cognitive function labels vital to any discussion of underlying synaptic plasticity (henceforth *learning/memory*): (1) the awareness and acquisition of new stimulus/response associations, episodic events, etc. (*attention/encoding*); (2) the deliberate recording and persistence of learned information (*storage/consolidation*); and (3) the recovery and expression of remembered information (*retrieval/recall*). These three labels are useful for dividing up the temporal stages in the learning/memory sequence (early, intermediate, and late) as well as for dissociating brain sites and nervous system signaling pathways involved in mobilizing changes necessary for one or more stages of the sequence (Martinez et al., 1991; Baddeley, 1995; Tonegawa et al., 2003). Thus, while the review of relevant literature is limited largely to recent research and theoretical advances appearing since the 1998 publication of the first edition, coverage is comprehensive, in the sense that the cognitive and neural mechanisms described herein can be thought of as least common denominators through which any valid learning/memory manipulation would likely exert its enhancing effect on performance (see Fig. 17-1).

Memory-fitness strategies to combat learning/memory loss represent a vitally important topic that has been addressed in book-length form by researchers as well as clinicians in the learning/memory field (Einstein and McDaniel, 2004; Small, 2004). However, this chapter presents an account of learning/memory function in normal, unimpaired organisms based on the assumption that the unperturbed nervous system provides the best possible context in which to establish rigorous evidence of cognitive enhancer efficacy. Morris and colleagues argue, for example, that distinct memory processes described in later sections of this chapter cannot be characterized easily by studying organisms with permanent brain damage or irreversible brain lesions (Morris et al., 2003). Even the interpretation of transient memory-impairing treatments such as protein synthesis inhibition is viewed as problematic by some investigators (Silva et al., 1998). Yet the overriding goal, as articulated elegantly by Sweatt, is to "focus on the essential, defining characteristic of the mechanism at the heart of memory" (Sweatt, 2003). Thus, the present focus on learning/memory enhancement in the normal, intact nervous system will be sharpened by not addressing the copious literature related to learning/memory impairment, amnestic drugs/traumas, or aging-related decline in cognitive capacity (Barch, 2004; Leonard et al., 2004; Lupien et al., 2005).

The credibility of manipulations claimed to enhance learning/memory performance as well as the appropriateness of expending scientific capital and effort in this pursuit are open to question (Gerlai, 2003). It is certainly true that effective clinical treatment of dementia accompanied by memory loss represents a pressing health care goal. However, this aim is completely different in character from the use of cognitive enhancers as lifestyle supplements (Bohn et al., 2003) intended to increase performance in "intact intellects" (individuals with no identifiable pathology) in an ethically and legally dubious manner (Whitehouse et al., 1997; Farah et al., 2004; Mehlman, 2004). This is true in spite of the fact that the neurobiological mechanisms of action would presumably be shared in the therapeutic and lifestyle applications of cognitive enhancers; this circumstance further strengthens the present focus on enhancement mechanisms themselves while leaving the implementation and application of this knowledge to the reader. Moreover, in order to provide examples of nonpharmacological, noninvasive means of achieving cognitive enhancement, three stress-related, physical exercise, and state-dependent mechanisms (a.k.a. mneumonotechniques) reported to benefit performance of learning/memory tasks are also provided in this chapter as a supplement to information on pharmacological enhancement strategies (a.k.a. pro-cognitive drugs).

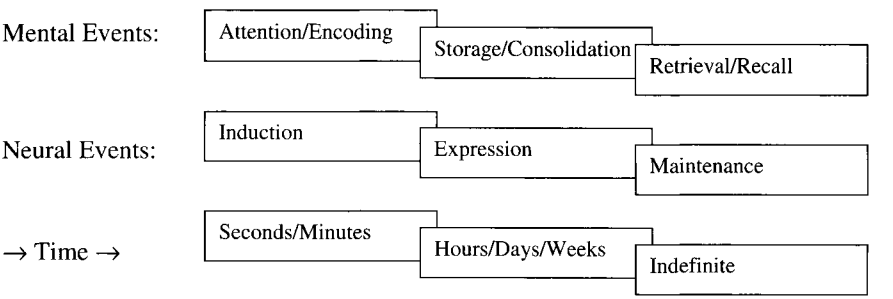

FIGURE 17-1 Schematic diagram relating the time course of mental and neural events underlying various inferred learning/memory processes. The first row labels essential components of the modal model of learning/memory performance. The second row labels presumed states of hippocampal long-term potentiation. The third row reflects evidence in multiple species for the timing of the various components of synaptic plasticity (Clayton, 2000; Dudai, 2004; Horn, 2004). The boxes overlap, and the time labels are coarse in order to reflect the lack of precise transitional boarders between the various entities. Indeed, the contribution of multiple learning/memory processes at the time of performance assessment may contribute to conflicting results in the literature (Barch, 2004). While the horizontal progression from left to right is very well worked out for each of the three rows, the vertical, column-wise linkages are only tentative and await further experimental work.

II. MECHANISMS OF ATTENTION/ ENCODING ENHANCEMENT

While therapeutic enhancement of cognitive function was once a topic for science fiction (Keyes, 1959), the neuroscience and clinical literature of the past few years provides ample documentation of basic brain mechanisms for and potential cognitive enhancement efficacy of pharmacological strategies tested in tasks sensitive to learning and memory performance (Buccafusco and Terry, 2000). The process of attention serves as an initial filter for discriminating novel stimuli during circumstances when organisms are required to shift from one perceptual dimension to another or to perform a reversal-learning sort of task (Dalley et al., 2004). The flexibility and accuracy of identifying target stimuli in a multiple-choice format is one attentional task that is dependent on prefrontal cortex function (Dalley et al., 2004). These processes reflect the earliest stages of mental activity necessary for successful learning/memory. Experimental studies have delineated later-occurring temporal phases of memory and synaptic plasticity including one short-lived form that is established soon after exposure to a novel stimulus and can be established in the absence of new mRNA and protein synthesis (Kelleher et al., 2004). This so-called *working memory* can be operationally defined as that store necessary for performing the current trial of a memory experiment but not for future trials, and like attention is also dependent on a functional prefrontal cortex (Dalley et al., 2004). It is critically important to note that treatments administered before training (i.e., initial learning) are capable of impacting all subsequent learning/memory stages (Martinez, 1986). However, little careful research is available to specify the exact point in time at which a particular cognitive enhancer mechanism is activated by an experimental treatment. Thus, learning/memory stage classifications for particular treatments listed later were assisted wherever possible according to neurobiological correlates that provide a supplemental index of the temporal characteristics of plasticity. Some pharmacological and behavioral strategies for the enhancement of attention to novel stimuli and the encoding of new memories (Fig. 17-2) are listed next.

A. Neuropharmacological Enhancements for Attention/Encoding

1. Dopamine Receptor Modulators

Discussion of pharmacological enhancement of learning/memory capacity ought to begin with a consideration of the utility of dopamine receptor modulators, given the enormous and long-standing influence of psychostimulant drug use to benefit attention and working memory (Goldman-Rakic, 1998; Leonard et al., 2004). Administration in monkeys of low doses of dopamine

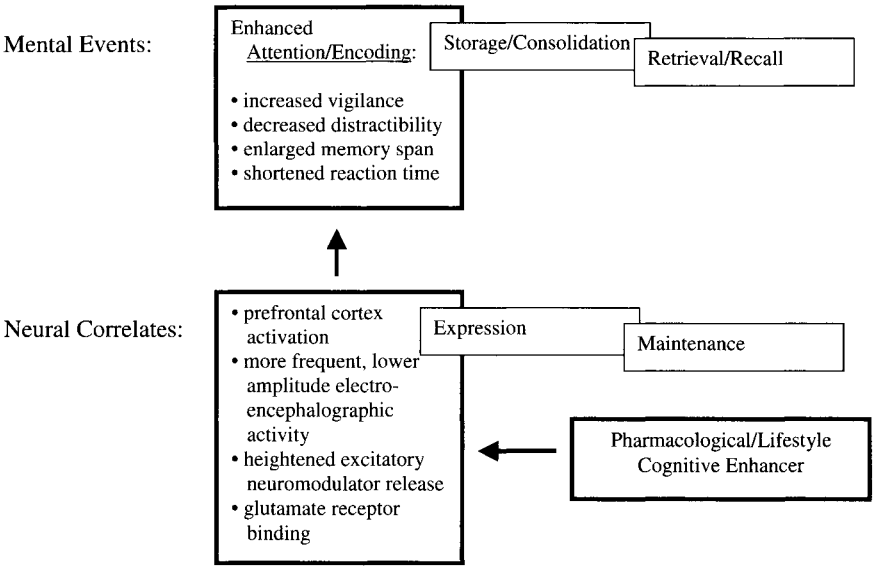

FIGURE 17-2 Schematic diagram relating the mental and neurobiological correlates of attention and encoding enhancement. Note that later-occurring mental and neural event labels are retained since there are likely proactive effects of attention/encoding enhancement on storage/consolidation and retrieval/recall of the same memory.

receptor agonists that result in an optimization of dopamine activation can improve performance of a working-memory task (Williams and Goldman-Rakic, 1995). This finding generalizes to healthy human participants administered nonselective dopamine receptor agonists, such as amphetamine and methylphenidate, which act to increase accuracy or shorten response latency in working-memory tasks (Barch, 2004). One study employed brain imaging to examine physiological correlates of the effects of dextroamphetamine on working-memory performance in healthy controls (Mattay et al., 2000). The catecholamine psychostimulant increased prefrontal cortex activation during a working-memory task performed at mnemonic capacity. However, dextroamphetamine improved performance only in participants who had relatively low working-memory capacity at baseline (Mattay et al., 2000). The degree of task-related enhancement of dorsolateral prefrontal cortex activity in response to amphetamine administration was associated with larger improvement in accuracy. Methylphenidate administration in healthy adults is also reported to enhance performance in a spatial pointing task, although marked individual differences are also reported (Leonard et al., 2004). Rather than direct mediation of the learning/memory trace, the nonspecific mechanism of cognitive enhancement via dopaminergic activation is presumed to be elevation of reward expectancy (Rossetti and Carboni, 2005). Thus, the hypothesis that

dopamine-augmenting agents can improve working memory is supported at the present time, and current research is focused on identifying dopamine receptor–selective agonists suitable for human administration (Barch, 2004).

2. Glutamate Receptor Modulators

A well-accepted model for a likely neurobiological mechanism involved in encoding at the earliest stages of learning involves two classes of transmitter receptors colocalized at excitatory, glutamatergic synapses (Horn, 2004). AMPA-type receptors generate depolarizing currents needed to disinhibit voltage-sensitive NMDA-type receptors, which then admit calcium into the dendrites on the postsynaptic side of the synapse (Lynch, 2002). One view is that increases in AMPA receptor number, recycling, or efficiency contribute to enhanced postsynaptic currents that define long-term potentiation, but only for a brief period of time (perhaps 30 minutes or less), following task acquisition/encoding.

So-called *ampakines* are allosteric modulators of AMPA receptors that enhance and prolong synaptic currents generated by release of glutamate from axon terminals (Lynch, 2002). Positive modulation of AMPA receptors can potentially enhance cognition by, first, offsetting losses of glutamatergic synapses; second, by promoting synaptic plasticity; and third, by increasing the production of trophic factors (Lynch, 2004). Ampakines affect only those AMPA receptors activated by endogenously released glutamate and thus only target active circuits. This functional selectivity is bolstered by the absence of ampakine sites of action outside of the central nervous system. The advent of small molecules that selectively enhance AMPA receptors in the brain has made it possible to test these hypotheses. For instance, a small-molecule ampakine capable of facilitating glutamate release in vitro is reported to improve significantly performance of a delayed matching-to-sample task by young adult rhesus monkeys, perhaps by accelerating memory encoding (Buccafusco et al., 2004). Ongoing clinical work (Marshal, 2004) reveals that young adult participants exhibit small-to-moderate improvements in tests of visual association, odor recognition, and visuospatial maze acquisition (Lynch, 2002).

3. Adenosine Receptor Antagonists

Caffeine is the most widely consumed central-nervous-system stimulant (Nehlig et al., 1992). Methylxanthines including caffeine act as adenosine receptor antagonists to activate noradrenaline neurons and alter the local release of dopamine. Behavioral measurements indicate a general improvement in the efficiency of information processing after caffeine consumption, while electroencephalographic data support the general belief that caffeine acts as a stimulant (Lorist and Tops, 2003). Studies using event-related potentials to measure the

timing and amplitude of cortical reactivity to stimulus presentation indicate that caffeine has an effect on attention, which is independent of specific stimulus characteristics. Thus, the effects of caffeine on learning/memory performance are likely related to methylxanthine enhancement of arousal and vigilance.

One study tested this potential link between consumption of caffeinated beverages and arousal (Ryan et al., 2002). Memory performance depends on the time of day, with performance being optimal early in the morning and declining during the late afternoon hours, and it is possible to examine whether this decline is ameliorated by the adenosine receptor antagonist caffeine (Ryan et al., 2002). Adults over the age of 65 who considered themselves "morning types" were tested twice using a list-learning test requiring both free recall and recognition, once in the morning and once in the late afternoon. Participants who ingested decaffeinated coffee showed a significant decline in memory performance from morning to afternoon. In contrast, those who ingested caffeine showed no decline in performance from morning to afternoon. The results suggest that time-of-day effects may be mediated by nonspecific changes in level of arousal (Ryan et al., 2002). This finding is not surprising from an epidemiological point of view, although it may be difficult to disentangle learning/memory modulatory effects of caffeine from self-medicating behaviors in a human population that is increasingly caffeine dependent or at least well experienced with the psychoactive efficacy of caffeine (Nehlig, 1999).

4. Nicotinic Receptor Agonists

The nicotinic acetylcholine receptor is a ligand-gated, Ca^{2+}-permeable channel that facilitates neurotransmitter release at presynaptic sites in the central nervous system (Hejmadi et al., 2003). Of particular interest for the study of synaptic plasticity, Ca^{2+} entry through nicotinic receptors on hippocampal mossy fiber terminals elicits bursts of excitatory postsynaptic currents. Nicotinic receptor activation also promotes a Ca^{2+}-dependent second-messenger cascade (i.e., protein kinase, ERK/MAPK, and CREB) that participates in long-term potentiation. Given the broad-spectrum transmitter and second-messenger modulatory actions of nicotine (Hejmadi et al., 2003), it is not possible to discern if some or all of these events participate in cognitive enhancement. However, nicotine-like ligands exert in several species a wide range of behavioral effects, including improvements in a variety of cognitive tasks, whereas nicotine receptor antagonists impair these functions (Rezvani and Levin, 2001). Nicotinic agonists are reported to be effective in reducing distractibility (i.e. facilitating attention to the task at the earliest possible stage of learning/memory) in young adult animals (Buccafusco and Terry, 2000). Administration in mice of a β4-nicotinic receptor agonist is reported to be dose-dependently effective in enhancing working memory in a delayed nonmatching-to-

place task using an eight-arm radial maze (Bontempi et al., 2003). The weight of evidence suggests that the nicotinic mechanism of action is sufficient to produce enhancement at the earliest processing stages of attention/encoding, although intermediate- and late-stage facilitation of storage/consolidation via facilitation of protein synthesis could also play an important modulatory role as time progresses.

In clinical studies, nicotine is known to increase cortical arousal, as measured electroencephalographically, which is thought to be associated closely with the quality of attentional efficiency. In order to elucidate the neural correlates of cognitive effects of nicotine, one study examined behavioral performance and blood oxygenation-dependent regional brain activity, using functional magnetic resonance imaging, during a working-memory task in healthy nonsmoking males after the administration of nicotine or saline (Kumari et al., 2003). Nicotine, compared to placebo, improved accuracy and shortened response latency under heavy memory load conditions. Nicotine activated the anterior cingulate, superior frontal cortex, and superior parietal cortices and midbrain tectum in all active conditions and the parahippocampal gyrus, cerebellum, and medial occipital lobe during a rest period. These observations point to altered neuronal activity in a distributed neural network associated with attention and arousal systems as a mechanism mediating nicotine enhancement of attention and working memory in humans (Kumari et al., 2003). Moreover, the hemispheric lateralization of activation as a function of nicotine dependence suggests that chronic exposure to nicotine or withdrawal from nicotine affects cognitive strategies used to perform a working-memory task (Ernst et al., 2001).

5. Neurosteroids

Neurosteroids, synthesized in the central and peripheral nervous systems from cholesterol or steroidal precursors (Baulieu et al., 2001), can alter rapidly neuronal excitability by nongenomic modulation of GABA and glutamate neurotransmission (Paul and Purdy, 1992). Two neurosteroids, pregnenolone sulfate (PREGS) and dehydroepiandrosterone (DHEAS), act as antagonists at GABA-A receptors and positively modulate NMDA receptor responses (Bergeron et al., 1996; Maurice et al., 1997). Evidence suggests a role for PREGS and DHEAS in improving performance of hippocampally mediated memory tasks, such as spatial recognition (Pallares et al., 1998; Darnaudery et al., 2000), Y-maze alternation (Mathis et al., 1996; Akwa et al., 2001), visual discrimination go/no-go (Meziane et al., 1996), and motivated lever-press learning (Mathis et al., 1996). PREGS and DHEAS are both effective at increasing learning and retention when administered pre- and posttraining, but not when administered just prior to retention testing in a passive-avoidance paradigm (Reddy and Kulkarni, 1998).

Several mechanisms could contribute to the promnestic actions of PREGS. One possibility is that PREGS enhances central cholinergic function, based on the observation that administration of PREGS in the nucleus basalis magnocellularis, the main source of cortical cholinergic innervation, improves memory performance of young rats (Pallares et al., 1998). Additionally, central administration of PREGS increases extracellular acetylcholine concentrations in the hippocampus (Vallee et al., 1997; Darnaudery et al., 2000). PREGS enhances NMDA-activated currents and inhibits GABA-mediated currents in cultured rat hippocampal neurons (Bowlby, 1993). These in vitro results are consistent with neuronal excitatory and convulsant effects of PREGS in vivo (Majewska et al., 1989). In addition, PREGS could influence NMDA and GABA-A receptor functions by a nonspecific action such as altering membrane fluidity (Nilsson et al., 1998). Pretraining efficacy in learning/memory contexts as well as glutamatergic mediation of neurosteroid actions are thus consistent with the classification of neurosteroids as attention/encoding enhancers.

6. Estrogen

The estrogens are a family of steroid hormones that regulate and sustain female sexual development and reproductive function. Besides affecting the hypothalamus and other brain areas related to reproduction, ovarian steroids have widespread effects throughout the brain, on serotonin pathways, catecholaminergic neurons, the basal forebrain cholinergic system, and the hippocampal formation. Ovarian hormones regulate synapse turnover in the CA1 region of the hippocampus during the four- to five-day estrous cycle of the female rat (Woolley et al., 1990). Formation of new excitatory synapses is induced by estradiol, involves NMDA receptors, and is mediated by acetylcholine (Daniel and Dohanich, 2001). It is also likely that estrogens locally regulate events at the sites of synaptic contact in the excitatory pyramidal neurons where the synapses form (McEwen, 2002). Estrogen interacts with the rat cholinergic system in numerous ways, such as enhancing cortical cholinergic enervation and preserving synaptic density following excitotoxic lesions in the basal forebrain (Horvath et al., 2002). Hippocampal long-term potentiation is facilitated by increased levels of circulating estrogen, as evidenced by the finding that cyclical changes in endogenous estrogen levels can augment long-term potentiation (Cordoba, Montoya, and Carrer, 1997; Good et al., 1999).

In rats, intrahippocampal infusions of estradiol potentiate acetylcholine- and glutamate-mediated memory retention in an avoidance-learning task (Farr et al., 2000). Estrogen administration results in improved performance in avoidance (Singh et al., 1994) and Morris water maze tasks (O'Neal et al., 1996). In intact male and female mice, chronic estrogen treatment improves radial arm maze working-memory performance (Heikkinen et al., 2002).

Additionally, estrogen-mediated improvement in radial maze working-memory is dependent on acetylcholine acting through M2 muscarinic receptors to increase NMDA receptor binding in the hippocampus (Daniel and Dohanich, 2001). These studies support the hypothesis that estrogen is a regulator of learning-related mechanisms. Further, evidence suggests that estrogen increases NMDA receptor activity, and this is likely a further mechanism through which it enhances long-term potentiation (Gureviciene et al., 2003). Broad involvement of estrogen in modulating synaptic plasticity is consistent with classification as an attention/encoding enhancer.

B. Everyday Attention/Encoding Enhancer: Stress–Cognition Axis

An introductory psychology textbook could characterize the adaptive relationship between stressor exposure and learning/memory functions by stating in so many words that "one who learns to run away lives to learn another day!" Specialist researchers also highlight the efficacy of emotionally salient stimuli in evoking long-lasting or particularly intense memories (Cahill, 2003). Moreover, the physiological and psychological consequences of acute and chronic activation of the hypothalamus, amygdala, and pituitary/adrenocortical glands are well-known modulators of learning/memory performance across the life span (Lupien et al., 2005). Noteworthy for the present discussion is the ability of these mechanisms to facilitate learning/memory of particularly salient, affectively significant events (McGaugh, 2003).

1. Hypothalamo-Pituitary-Adrenocortical Peptides and Steroids

Stress and behavioral plasticity are interrelated; levels of alertness correspond to success in performance of a learning task in what can be described as the "stress–cognition" axis (Heinrichs, 1999). Stressors, circulating stress-related hormones, and central nervous system releasing factors that facilitate the pituitary-adrenocortical cascade all modulate learning/memory processes. One study characterized the action of an acute immobilization stressor on hippocampus-dependent learning and synaptic plasticity in the mouse hippocampus (Blank et al., 2003). Acute stress facilitated long-term potentiation of population spikes and enhanced context-dependent fear conditioning. Due to the involvement of hippocampus and induction of long-term potentiation, which are characterstic of early-stage learning/memory processing, stressor exposure can be classified as an attention/encoding enhancer. However, acute stress-induced enhancement of long-delay retrieval performance has also been demonstrated following exposure to a species-typical social stressor (Fig. 17-3).

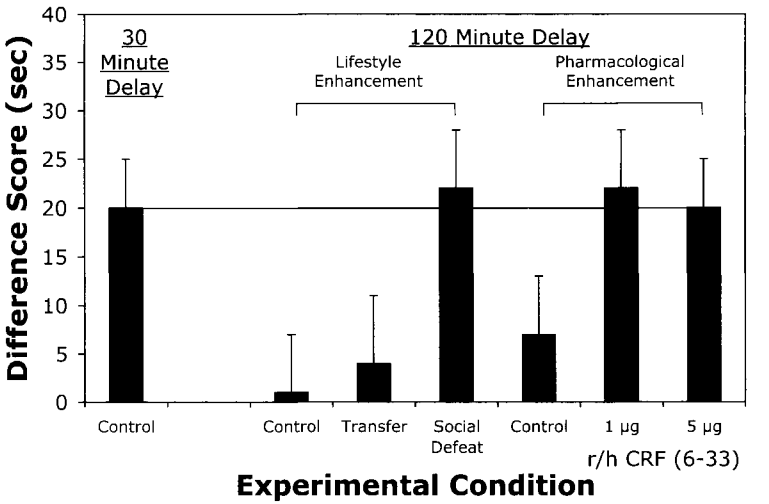

FIGURE 17-3 Social defeat and stress neuropeptide activation enhance social recognition memory. Female rats taken directly from the home cage, transferred to a holding cage, exposed previously to a social defeat stressor, or administered 0-, 1-, or 5-µg doses of the CRF-binding protein ligand inhibitor were allowed to investigate a juvenile conspecific. The duration of adult exploration of the juvenile on first presentation relative to the second presentation of the same juvenile either 30 minutes later (short delay) or 120 minutes later (long delay) was used to compute a difference-score measure (mean ± SEM) of social recognition memory. The attenuation of poor performance in the long-delay condition by prior exposure to the social defeat stressor or two doses of CRF-binding protein ligand inhibitor was used as the index of memory enhancement (Heinrichs, 2003). Cognitive enhancers are often evaluated using long training-to-test intervals (i.e., at the mnemonic limit), as in the present case, so that the degree of baseline performance restoration can be assessed (Buccafusco and Terry, 2000).

The glucocorticoids are a group of adrenocortical steroid hormones whose metabolic effects include stimulation of gluconeogenesis, increased catabolism of proteins, mobilization of free fatty acids, and potent inhibition of the inflammatory response. In addition, the effect on learning capacity of chronic activation of the hypothalamo–pituitary–adrenal axis has been characterized using long-term peripheral administration of glucocorticoids in mice, rats, monkeys, and humans (Lupien et al., 2005). In particular, glucocorticoid administration alters acquisition of a previously unlearned task in a dose-related, inverted-U-shaped fashion (de Kloet et al., 2002). The amygdala, which expresses high levels of adrenal steroid receptors, is a malleable brain structure that is important for certain types of learning and memory (McEwen and Chattarji, 2004). Repeated stress promotes behavioral changes, such as enhancement of fear and aggression, that can be associated with this brain structure. At a cellular level, fear conditioning elicits growth and remodeling of dendrites in the lateral amygdala (McEwen and Chattarji, 2004). Thus,

short-term exposure to physiological levels of exogenous glucocorticoids could be expected to enhance performance in a learning and memory context, and this hypothesis is supported by animal and human clinical studies (Buchanan and Lovallo, 2001; McGaugh and Roozendaal, 2002). One prediction from the correlational link between the level of arousal and performance of learned behaviors is that intrinsic overactivation and/or long-term stimulation of neurobiological and endocrine substrates of the stress response would have the effect of producing learning and memory deficits, and this corollary hypothesis is also supported by available data (Lupien et al., 2005).

Corticotropin-releasing factor (CRF) is recognized widely as part of a neuropeptide system whose activation is a necessary component of the biological response to stressor exposure (Heinrichs and De Souza, 2001). Evidence supports a physiological role for CRF systems in information-processing functions of the central nervous system. First, steady-state levels of endogenous CRF family neuropeptide receptor agonists appear sufficient to modulate learning/memory functions, since pharmacological dissociation of CRF and a related neuropeptide, urocortin, from their binding protein enhances performance (Fig. 17-3) in appetitively and aversively motivated memory tasks (Behan et al., 1995a; Heinrichs et al., 1997; Eckart et al., 1999; Zorrilla et al., 2001). In addition, central CRF administration exerts electrophysiological and neurochemical activation of hippocampal circuits relevant for learning/memory processes in several species (Bonaz and Rivest, 1998; Wang et al., 1998; Fuchs et al., 2001). These findings suggest that CRF activation is sufficient to ensure that the early states of learning/memory plasticity are set in motion (Fig. 17-4). This conclusion is supported by results indicating that CRF, adrenocorticotropic hormone, and glucocorticoids continue to be significant modulators of learning and memory processes when either the organism or the treatment itself is rendered incapable of pituitary-adrenocortical activation (Honour and White, 1988). Thus, peptides and steroid hormones of the HPA axis, such as CRF and glucocorticoids, are presumed to be the neurochemical modulators of enhanced long-term memory for stressful or emotionally arousing experiences (Roozendaal, 2002). The pharmacological (Behan et al., 1995b), neurobiological (Radulovic et al., 2000), and clinical (Bernardi et al., 2000) evidence necessary to support this claim convincingly is only now being assembled.

III. MECHANISMS OF STORAGE/ CONSOLIDATION ENHANCEMENT

The process of postacquisition stabilization of long-term memory, labeled *consolidation*, is still germain, in spite of the age-old vintage of this concept (McGaugh, 2000; Dudai, 2004). The term *systems consolidation* can be defined as the process by which memory becomes independent of the hippocampus,

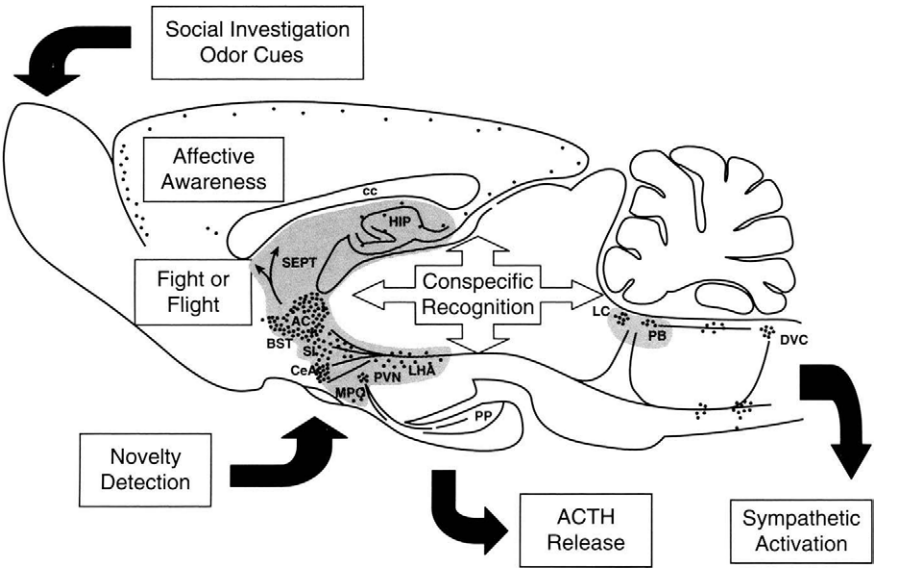

FIGURE 17-4 Schematic diagram of CRF/urocortin brain activity in which the rat detects a conspecific olfactory cue that is recognized as a familiar/unfamiliar juvenile during social investigation while performing the social recognition memory task. CRF/urocortin-mediated efferent responses to threat could include hypophysiotropic release of ACTH, amygdalo-medullary increases in heart rate, septo-hippocampal avoidance learning, and septo-amygdalar anxiogenic-like behavior (Heinrichs and Koob, 2004). AC, anterior commissure; ACTH, adrenocorticotropic hormone; BST, bed nucleus of the stria terminalis; cc, corpus callosum; CeA, central nucleus of amygdala; DVC, dorsal vagal complex; HIP, hippocampus; LC, locus coeruleus; LHA, lateral hypothalamus; MPO, medial preoptic area; PP, posterior pituitary; PVN, paraventricular nucleus; SEPT, septum; SI, substantia innominata.

whereas *cellular consolidation* is defined as the transition of memory traces from protein synthesis and gene expression–dependent states to independence (Dash et al., 2004; Dudai, 2004). The hallmarks of the consolidation process are (1) relocation from short-term hippocampal memory stores to distributed neocortical networks and (2) the gradual, time-dependent process of laying down long-term memories, in which the most recent memories are the most fragile (Sara, 2000). The intermediacy of storage/consolidation can be further delineated by stipulating that this learning/memory stage does not employ any sensorimotor faculties or rely on short-term memory, as does the attention/encoding stage described earlier (Dudai, 2004). The mechanism for storage is hypothesized to be the transit of synthesized proteins via axonal transport to, or induction of gene products in, extra-hippocampal synapse assemblies that are distinguished from all other potential neural assemblies by prior synaptic activity in the tagged locations. Activation of cell-signaling cascades and

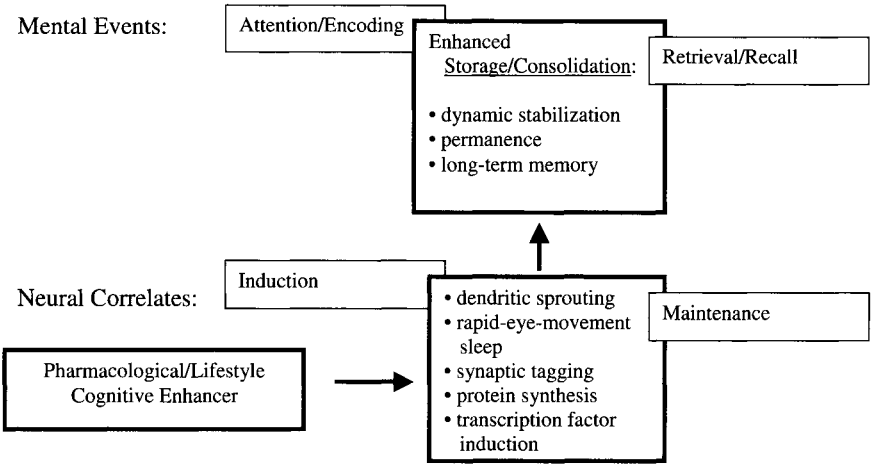

FIGURE 17-5 Schematic diagram relating the mental and neurobiological correlates of storage and consolidation enhancement. Note that earlier- and later-occurring mental and neural event labels are retained, since there are likely proactive, carryover effects of storage/consolidation enhancement on retrieval/recall of the same memory as well as carryover effects of original storage/consolidation on subsequently occurring learning/memory events.

phosphorylated transcription factors, termed the *genomic action potential* (Clayton, 2000), appear to be proximal mediators of cellular consolidation processes that can be identified in relevant hippocampal, limbic, and cortical regions following conditioning in animals. The elegance of this dynamic, distributed information-storage mechanism provides a fitting resolution to Lashley's experimental quandary in which a localized "engram" proved difficult to isolate using progressive cortical ablation methodologies (Lashley, 1958). Some pharmacological and behavioral strategies for enhancing storage and consolidation of memories (Fig. 17-5) are listed next.

A. Neuropharmacological Enhancements for Storage/Consolidation

The use of treatments administered shortly after training to enhance memory provides a highly effective method of influencing memory consolidation without necessarily affecting either attention/encoding or retrieval/recall (McGaugh, 2000). For example, daily pretraining administration in rats of the general stimulant strychnine increases the rate of maze learning in rats (McGaugh and Krivanek, 1970). The possibility that apparent increases in learning/memory were attributable to drug-induced increases in running speed or other performance changes characteristic of acute drug intoxication (including potential enhancement of early-state attention/encoding processes) were

ruled out by the finding that posttraining administration of strychnine also facilitated learning performance during the next day's trial, when rats were tested in a drug-free state.

1. *Adrenergic Neurotransmission*

Epinephrine and drugs that activate adrenergic receptors enhance memory for many kinds of training experiences (McGaugh, 2000). For example, β-adrenergic agonists infused after training either systemically or directly into the basolateral amygdala enhance learning/memory performance. The literature also supports the ability of α_2 noradrenergic receptor agonists to facilitate learning/memory performance. For instance, administration of the α_2 noradrenergic receptor agonist clonidine in healthy adults improves performance in a spatial pointing task in a dose- and practice-dependent manner (Coull et al., 1997). Pharmacological enhancement via noradrenergic receptor agonist treatment is likely mediated by activation of a locus coeruleus to forebrain noradrenergic pathway associated with increased accuracy of response to task-relevant stimuli (Aston-Jones et al., 2000). Levels of noradrenaline in prefrontal cortex increase when rats perform correctly in a delayed variant of a spatial working-memory task (Rossetti and Carboni, 2005). Tellingly, noradrenaline levels were markedly enhanced in animals trained to alternate as compared with rats that acquired the spatial information about the location of food in the maze but were untrained to make a choice to obtain the reward. One study investigated the effect of enhanced noradrenergic activity on memory consolidation in humans (Southwick et al., 2002). Thirty participants viewed a series of slides that depicted an emotionally arousing story. Multiple blood samples were drawn for determining plasma levels of the noradrenaline metabolite MHPG. One week later, participants completed an unannounced memory test for the slides. Linear regression revealed a significant effect of MHPG on memory score for the group as a whole. These findings strengthen support for the hypothesis that enhanced memory for emotionally arousing events in humans depends critically on postlearning adrenergic modulation (Southwick et al., 2002). A more general conclusion is that noradrenergic neurotransmission is required for active maintenance and flexible manipulation of learned information during successful goal-seeking behavior. The classification of adrenergic modulation as a storage/consolidation enhancer is based on nonhippocampal distribution of noradrenergic circuitry in the brain as well as the relatively large literature describing posttraining efficacy of noradrenergic receptor ligands.

2. *Trophic Factors*

Nerve growth factor (NGF) is a multimeric protein, the beta subunit of which is required for the proper development and maintenance of the sensory neurons

of the dorsal root ganglion and of the postganglionic sympathetic neurons. NGF-induced facilitation of learning/memory performance is supported by efficacy of NGF treatment in a variety of animal species and testing contexts. In a classical fear-conditioning task, endogenous NGF is reported to increase one week after training (i.e., during the consolidation phase), while infusion of antisense for the NGF receptor (TrkA) in the hippocampus one week post-training can block this retention (Woolf et al., 2001). In developing CD-1 mice, a single intracerebroventricular administration of NGF at postnatal day 15 resulted in adultlike spatial novelty discrimination in males but not females tested at postnatal day 18, although increased choline acetyltransferase activity was observed in both sexes as a result of NGF treatment (Calamandrei et al., 2002). The link between NGF and cholinergic activity is supported by the observation that the effects of NGF on recent memory in the delayed non-matching-to-position task correlate with changes in the cholinergic system, including increased size of cholinergic neurons and a change in the terminal fields of these same neurons (Gustilo et al., 1999). Taken together, these results suggest that central administration of exogenous NGF can facilitate learning/memory consolidation while remodeling cholinergic brain areas thought to subserve synaptic plasticity.

Brain-derived neurotrophic factor (BDNF), an NGF-related neurotrophin with high affinity for the TrkB receptor, is known to have numerous roles in learning and memory and contributes to the process of hippocampal long-term potentiation (Tyler et al., 2002; Yamada et al., 2002). Both long-term potentiation and spatial learning are associated with increased phosphorylation of TrkB (BDNF receptor) and extracellullar signal-regulated kinase (ERK) in the dentate gyrus following administration of BDNF (Gooney et al., 2002). Although it is still unclear whether BDNF exerts housekeeping functions to maintain neuronal functioning, BDNF appears to play an important role in long-term potentiation induction and modulation (Kovalchuk et al., 2002; Messaoudi et al., 2002). The specific mechanism of BDNF-mediated long-term potentiation, which is induced postsynaptically (Kovalchuk et al., 2002), suggests that BDNF interacts directly with NMDA receptors to increase their activity (Mizuno et al., 2003). Mnemonic effects of BDNF are found in rodents, in primates, where the peptide is up-regulated in the inferior temporal cortex during visual pair-association learning (Tokuyama et al., 2000), and in day-old chicks, where BDNF antisense administration impairs memory consolidation in a one-trial inhibitory-avoidance paradigm (Johnston and Rose, 2001). Lee and colleagues argue for a specific role of BDNF in long-term learning/memory consolidation, based on the ability of BDNF antisense administration into dorsal hippocampus to impair performance in a contextual fear-conditioning task (Lee et al., 2004). In contrast, BDNF knockdown had no effect on the encoding of associative memory because short-term memory was normal three hours after training. Thus, the weight of evidence for NGF

and BDNF efficacy when administered posttraining, often with a substantial delay, and a general neural modulatory role independent of the hippocampus allows classification of trophic factors as putative storage/consolidation enhancers.

3. Cholinergic Neurotransmission

For more than 20 years, the ability of drugs, such as physostigmine, that enhance synaptic levels of acetylcholine to facilitate learning/memory recall has been recognized (Deutsch, 1983; Robbins et al., 1997). One report describes a randomized, double-blind, parallel group, placebo-controlled study to test the effects of the acetylcholinesterase inhibitor donepezil on aircraft pilot performance in healthy, middle-aged, licensed pilots (Yesavage et al., 2002). After 30 days of treatment, the donepezil-treated group showed greater ability to retain the capacity to perform a set of complex simulator tasks than the placebo group. Thus, donepezil appears to have beneficial effects on retention of training of complex aviation skills in nondemented, older adults. The hypothesis that enhancement of cholinergic transmission facilitates learning/memory processes (typically referred to as the *cholinergic hypothesis* when referencing therapeutic approaches for dementing disorders) is supported by a broad efficacy of cholinomimetic agents testing in learning/memory contexts (Buccafusco and Terry, 2000). Cholinergic enhancement also facilitates visual attention by increasing activity in extrastriate and prefrontal cortices (Furey et al., 2000; Bentley et al., 2004); see also the earlier section on "Nicotinic Receptor Agonists" as attention/encoding enhancers. High levels of acetylcholine present during active encoding of new information in the hippocampus suggest a role for cholinergic neurotransmission in learning/memory consolidation (Hasselmo, 1999).

B. Everyday Storage/Consolidation Enhancer: Exercise/Activity

Studies of adult animals indicate that metabolic and neurochemical functions improve with aerobic fitness. For example, the effects of physical activity on hippocampal cholinergic function, parietal cortical cholinergic function, and spatial memory have been examined in rats (Fordyce and Farrar, 1991). Three weeks prior to the end of the 14-week chronic treadmill-running protocol, a group of chronic-run rats and their nonrun controls were tested on a stringent version of a place-learning-set task. Chronic-run rats exhibited enhanced performance on the spatial task by significantly reduced second-trial latencies and elevated first- and second-trial proximity ratio scores. Chronic-run rats tested for spatial memory also showed enhanced hippocampal high-affinity choline uptake and muscarinic receptor binding (Fordyce and Farrar, 1991). An

additional study from this group supported the hypotheses of enhanced hippocampal PKC activity in spatial learning and enhancement of spatial learning performance in rodents by physical activity (Fordyce and Wehner, 1993). These data indicate that chronic physical activity improves spatial learning performance, which is correlated with enhancement of hippocampal plasticity.

A review of studies assessing the effects of acute bouts of physical activity on cognitive performance in healthy adults reveals that submaximal aerobic exercise performed for periods up to 60 minutes in duration facilitates specific aspects of information processing (Tomporowski, 2003). One study followed 124 previously sedentary adults over a six-month period of either aerobic exercise (walking) or anaerobic exercise (stretching and toning) (Kramer et al., 1999). Participants who received aerobic training showed substantial improvements in performance on tasks requiring executive control (e.g., task switching and the ability to ignore task-irrelevant stimuli) relative to the anaerobic comparison group. In support of the role of tropic factors in synaptic plasticity, long-lasting expression of BDNF and TrkB in cerebellum, motor cortex, and hippocampus can be induced by exercise and complex acrobatic training (Klintsova et al., 2004). Moreover, voluntary wheel-running exercise can reverse a high-fat-diet-induced decrement in BDNF and its downstream plasticity effectors (Molteni et al., 2004). Thus, physical activity appears to enhance learning/memory performance in a cholinergic and neurotrophic factor–dependent manner, consistent with a storage/consolidation mechanism of action.

IV. MECHANISMS OF RETRIEVAL/ RECALL ENHANCEMENT

A brainwide distributed network orchestrates the recall and retrieval of explicit memory (i.e., memory of facts and events). The network was initially identified in humans and is being investigated systematically in molecular/genetic, single-unit, lesion, and imaging studies in animals (Miyashita, 2004). The unique association between environmental stimuli and context depends on neural activation in the medial temporal lobe (i.e., hippocampus and associated regions), whereas memory traces representing repeated associations reside in domain-specific regions in the temporal cortex. These regions are reactivated during remembering and contribute to the contents of a memory (Fig. 17-6). Note that the functional neuroanatomy of human memory retrieval based on brain-imaging studies is unexpected, based on evidence derived from brain-lesion studies (Fletcher et al., 1997), hence supporting the focus on the healthy, normal nervous system in the present chapter and highlighting the need for convergent neuropharmacological evidence described next.

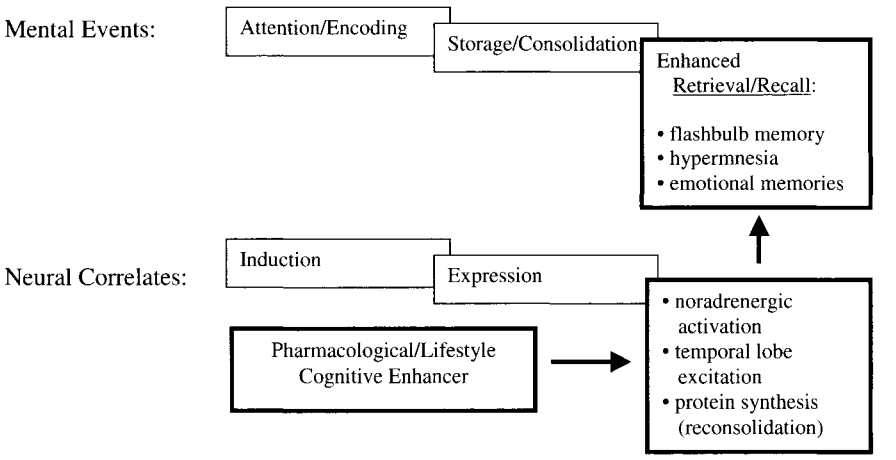

FIGURE 17-6 Schematic diagram relating the mental and neurobiological correlates of retention and recall enhancement. Note that earlier-occurring mental and neural event labels are retained, since there are likely carryover effects of original retrieval/recall enhancement on subsequently occurring learning/memory events.

A. Neuropharmacological Enhancement of Retrieval/Recall

There are relatively few pharmacological studies of direct effects of drugs on memory retrieval (Sara, 2000). Agents reported to exert retrieval enhancement include strychnine, cocaine, nootropics such as piracetam, and nicotine (three of these four agents were discussed in previous sections of this chapter). Efficacy can be selective in the case of amphetamine, which facilitates retrieval of a forgotten maze task, without affecting task performance when administered prior to or immediately following acquisition trials. The hypothesized mechanism of action for psychostimulant drug–induced facilitation of retrieval performance is increased arousal or vigilance (White and Salinas, 1998). Some pharmacological and behavioral strategies for enhancement of retrieval or recall of learned information (Fig. 17-6) are listed next. Note that coming as it does at the end of a long sequence of learning/memory stages, retrieval/recall enhancement is increasingly difficult to dissociate from earlier activated learning/memory mechanisms — hence a relatively diminished number of retrieval/recall enhancers are discussed and in a more guarded fashion at that.

1. Serotonin Neurotransmission

Substantial evidence indicates that serotonin receptors are involved in the regulation of acetylcholine release in brain regions important to mnemonic processes, and they may thus be exploited pharmacologically as targets for

memory improvement (Terry et al., 1996). In a series of studies, potent serotonin receptor agonists have been evaluated for potential memory-enhancing effects in macaque monkeys trained to perform a delayed matching-to-sample task (Terry et al., 1998, 2004). For example, serotonin 5HT3 receptor antagonists and 5HT4 receptor agonists appear to be efficacious cognitive enhancers (Terry, 2004). Improvements above baseline are typically observed in medium- and long-delay conditions, suggesting that the mechanism of serotonin receptor stimulation is selective enhancement of retention under conditions of poor performance.

B. Everyday Storage/Consolidation Enhancer: State-Dependent Retrieval

Drug-induced-state–dependent learning as well as similar effects on memory retrieval exercised by physiological states have been known since 1830 (Overton, 1991). The main finding is that memories can be retrieved only when a common, particular emotional or neurohumoral state is established both at the time of acquisition and at the time of expression (Izquierdo, 1989). In so-called *state-dependent* retrieval, awareness of a discriminable physiological state is efficacious in enhancing retention of information learned previously while in the same physiological state. Pharmacological cues such as psychostimulant, sedative, and opiate drugs are quite effective in enhancing retention of an arbitrary learning task if present at the time of retention testing, relative to the poor retention demonstrated during retention testing in the absence of the drug. For example, morphine-induced state-dependent learning has been investigated in animal models. Pretraining administration of morphine dose-dependently decreased the learning of a one-trial passive-avoidance task, whereas pretest administration of morphine-induced state-dependent retrieval of the memory acquired following pretraining administration of morphine (Zarrindast and Rezayof, 2004). Moreover, successful retrieval appears to become increasingly morphine dependent with repetition (Bruins, Slot, and Colpaert, 2003). Endogenous stress-related hormones, such as ACTH, vasopressin, and epinephrine, are effective in creating an easily discriminable internal state that can exert state-dependent retrieval benefits on performance (a.k.a. mood-congruent effect), although higher-order state variables, such as social rank and aerobic exercise, are also reported to be effective retention enhancers (Miles and Hardman, 1998; Barnard and Luo, 2002). Thus, state-dependent learning is a phenomenon in which the retrieval of newly acquired information is possible only if the organism is in the same sensory context and physiological state as during the encoding phase.

A cellular mechanism for the extensive behavioral and pharmacological characterization of the state-dependent-learning phenomenon has recently

been proposed. In this model, state-dependent learning is imposed in cortical neurons that exhibit acetylcholine-induced functional plasticity (Shulz et al., 2000). This was demonstrated using neurons of rat somatosensory cortex tuned to the temporal frequency of whisker deflections. Pairing whisker stimulation with acetylcholine applied iontophoretically yielded selective lasting modification of responses, the expression of which depended on the presence of exogenous acetylcholine. Administration of acetylcholine during testing revealed frequency-specific changes in response that were not expressed when tested without acetylcholine or when the muscarinic antagonist atropine was applied concomitantly (Shulz et al., 2000). These results suggest that learning/memory recall can be controlled by the cortical release of acetylcholine.

V. CONCLUSIONS AND FUTURE DIRECTIONS

An increasing number of structurally heterogeneous compounds, which may act via very different neuronal mechanisms, have been proposed to facilitate attention and acquisition, storage, and retrieval of information (Sarter, 1991). The cognitive enhancers just described fall into two general classifications of action: (1) direct mediators, such as glutamatergic agents, which are capable of adjusting the machinery of synaptic plasticity in which the mediator participates directly, and (2) modulators, such as adrenergic agents, which modify diffuse networks of neurons to adjust up or down the induction or expression of synaptic plasticity in an indirect manner without comprising a necessary component of the machinery of that plasticity (Clayton, 2000). It should be noted that a host of other putative cognitive-enhancement mechanisms that were omitted from this chapter likely exert efficacy via common upstream learning/memory modulator systems in a nonspecific fashion. For example, one could rightly suppose that direct neuropharmacological actions of treatments that regulate energy balance, such as neuropeptide Y and insulin, exert their long-term effects on cognitive function by indirect stimulation of glucose availability (Wenk, 1989). It would *not* be appropriate to conclude, however, that learning/memory performance in a reaction-time task was enhanced or impaired due to ergogenic or paralytic effects, respectively, of a treatment on muscle reactivity. This problem of specificity has been called one of the most difficult in learning and memory research (Martinez et al., 1983; Lombardi and Weingartner, 1995; Barco et al., 2003) and can be pursued in the future by defining the number and identity of unique mechanisms in local brain areas for optimizing learning and memory capability separate from other cognitive functions (Lombardi and Weingartner, 1995). Systematic coupling of functional efficacy with known neurobiological mechanisms for cognitive enhancement is one strategy employed in this chapter to work toward this goal (see Table 17-1).

TABLE 17-1 Prominent Anatomical, Physiological, Neurochemical, and Molecular Mediators of Early-, Intermediate-, and Late-Stage Learning/Memory Enhancement

Substrate	Attention/Encoding	Storage/Consolidation	Retrieval/Recall
Anatomical	Prefrontal cortex	Basolateral amygdala	Medial temporal cortex
Physiological	Presynaptic facilitation	Long-term potentiation	Metabolic activation
Neurochemical	Nicotinic receptors	NMDA/AMPA receptors	Noradrenergic receptors
Molecular	Immediate-early genes	CREB	MAPK

Of particular concern to the applied scientist is the process of rational target selection from among the many candidate learning/memory mediators/modulators known presently to be efficacious (Martinez et al., 2004). The isolation of a particular target as an essential link in the synaptic plasticity/gene expression/protein synthesis cascade may not confer on the mechanism utility for safe and selective cognitive enhancement. For example, the transcription factor CREB is argued *not* to be a particularly viable candidate for cognitive enhancement, since this signaling system is essential to many nonlearning/memory-related functions of the nervous system that would be impacted by general administration of a CREB-related drug (Barco et al., 2003). Similarly, it is unlikely that treatments that impact learning/memory performance as modulators of motivation or arousal, for example, could prevail over the inevitable pharmacological-side-effect profile that would accompany exposure to a candidate drug such as amphetamine (White and Salinas, 1998). The most promising cognition-enhancement strategies at the present time are replacement therapies, in which a depleted hormone or neurochemical is restored, estrogen therapy in postmenopausal women or cholinergic enhancement in Alzheimer's disease, for example (Resnick and Maki, 2001; Terry and Buccafusco, 2003). To the consternation of neuroscientists everywhere, the most productive and carefree strategies for selective and physiologically optimal cognitive enhancement in normal-functioning individuals may ultimately turn out to be environmental enrichment, physical exercise, or dietary changes in lifestyle.

One important utility for neurobiological mechanisms of synaptic plasticity is to quantify the magnitude of potential increase in learning/memory capacity that is or can be expected via mechanisms of cognitive enhancement. One pessimistic view is that existing enhancement strategies exert modest effect sizes on the order of 10–20% improvement (Buccafusco and Terry, 2000) and that this is the maximum expected enhancement using a pharmacological approach given inherent nonspecific drug actions (White and Salinas, 1998). On the other hand, Lisman argues for a graded state of synaptic activation that accom-

modates a range of values from "silent" through "disinhibited" to "potentiated" and describes how temporal parameters within a long-term-potentiation experiment can be adjusted to achieve higher levels of activation (Lisman, 2003). Indeed, at the cellular consolidation level of analysis, synaptic plasticity can be viewed as a mathematical certainty, based on the concentration of interacting synaptic proteins (Clayton, 2000). While synaptic activation can be considered as a necessary prerequisite in order for learning/memory substrates of the nervous system to operate, a further and more rigorous extension of this criterion would require that the degree of activation match the span, persistence, or accuracy of learning/memory performance. In contrast, a mismatch of perpetual or overly robust synaptic plasticity in the absence of incoming afferent information may produce high noise-to-signal ratios, which are associated with deleterious consequences in animal and insect learning/memory models (Barco et al., 2003) or "cognitive chaos" in humans (McGaugh, 2003).

Can reserve learning/memory capacity present in the nervous system and exploitation of this reserve via effective cognitive enhancement be considered adaptive from an evolutionary point of view? From a neuroethological perspective, the ability to conserve information about changing environmental or predatory threats for an extended period of time following a particular incident can be tremendously beneficial for the survival of an organism (Clayton, 2000). On the other hand, enhancements in the ability to recall autobiographical events, sometime referred to as *hypermnesia* (Bluck et al., 1999), can be considered obtrusive or pathogenic when inhibitory mechanisms break down (McNaughton and Wickens, 2003; Osman et al., 2004). The clinical case study of Luria's patient presented at the beginning of this chapter's introduction illustrates this point. One example of a potential pathological consequence of overly efficient recall is the flood of traumatic memories symptomatic of post-traumatic stress disorder (Layton and Krikorian, 2002). Similarly, it may be prudent to remain mindful of the inverted-U-shaped curve that typically governs the relationship between dose of a particular pharmacological cognitive enhancer and performance, lest an overused learning/memory-improvement strategy begins to have adverse consequences (Martinez et al., 1991; Barch, 2004; Lupien et al., 2005).

The search for drugs that enhance learning/memory requires the development and refinement of behavioral tests for animals (Olton and Wenk, 1990; Barnes, 2003; Morris et al., 2003). These tests must be able to identify potentially therapeutic treatments and reject ineffective enhancement strategies. Therefore, a coherent conceptual and experimental framework is needed to organize future research in this area (Brown et al., 2000). Unfortunately, previous preclinical research strategies appear to have focused on the demonstration of enhancing effects in a wide variety of tests of uncertain validity, rather than on determination of the specific psychological and neurobiological processes affected by putative cognition enhancers (McDaniel et al., 2003). For example, some sort of noxious stimulus, such as electric shock delivered

unexpectedly to rodent paw pads or escape from a water bath, is typically used to motivate learning in the widely used avoidance-conditioning (Uvnas-Moberg et al., 2000) and Morris-maze (Meijer et al., 2005) contexts, in spite of the fact that shock exposure and forced swimming produce an unconditioned affective state that can confound interpretation of learning performance in the task (Penka et al., 2004). A further disincentive for employing alarming and traumatic stimuli in the conditioning environment is provided by behavioral and cognitive neuroscience studies demonstrating that the affective salience of stimuli can bias encoding and retrieval of learned information in an automatic manner (Ochsner, 2000; Cardinal et al., 2002). Thus, future efforts require explicit identification of the goals of the research, the cognitive process, the neural systems and cellular gene products involved in the phenomenon, the selectivity and sensitivity of tasks that measure the process, and the validity of the behavioral tasks as a model to predict the effects of the cognitive-enhancement strategy in humans.

In conclusion, the present learning/memory classification scheme, based on evidence from cognitive psychology, has proven to be a useful rubric for distinguishing temporally and conceptually a variety of neurobiological events that presumably underlie synaptic plasticity. The linkage is not one to one, however, because events characterized in this chapter as influencing primarily the process of attention (e.g., general arousal) can certainly carry over to impact later consolidation and retrieval stages; an example of this nonspecific involvement at several steps in the process is state-dependent learning, in which, by definition, coordinated activation at two separate learning/memory stages is required. Similarly, changes in gene expression occasioned by some original learning/memory event can certainly impact encoding of any later-occurring event. The complexity of multifactorial enhancement will only increase with the emergence of mnemonic drugs acting at multiple targets in the nervous system (Buccafusco and Youdim, 2004).

VI. SUMMARY

1. Improvement in normal learning/memory performance using a so-called *enhancement neurology* approach is an achievable, if ethically dubious, goal.

2. Memory-fitness strategies to combat learning/memory loss represent a vitally important topic for public health.

3. An encoding/consolidation/retrieval classification scheme is a useful rubric for distinguishing temporally and conceptually a variety of neurobiological events that presumably underlie enhancement of synaptic plasticity.

4. Early-stage attentional and working-memory functions appear to benefit from optimization of dopaminergic, glutamatergic, nicotinic, and adenosinergic neurotransmission.

5. Neuro-, gonadal, and adrenal steroid systems appear to modulate early-stage encoding via indirect actions on other neurochemical and stress neuropeptide learning/memory mediators.

6. Intermediate-stage consolidation and learning/memory storage functions appear to benefit from optimization of adrenergic, trophic factor, and cholinergic neurotransmission.

7. Physical activity appears to enhance learning/memory performance in a cholinergic and neurotrophic factor–dependent manner consistent with a storage/consolidation mechanism of action.

8. Late-state memory recall and retrieval functions appear to benefit from optimization of serotonergic neurotransmission and from reexposure to subjective states present at the time of initial learning.

9. Cognitive enhancers include direct mediators, such as glutamatergic agents, which adjust the machinery of synaptic plasticity in which the mediator participates directly, and modulators, such as adrenergic agents, which modify diffuse networks of neurons to adjust synaptic plasticity in an indirect manner.

10. Given the difficulty in achieving specificity of pharmacological action, the most productive and carefree strategies for selective and physiologically optimal cognitive enhancement in normal-functioning individuals may ultimately turn out to be lifestyle changes.

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GLOSSARY

Acetylcholine — A neurotransmitter involved in learning/memory functions.

Ampakine — Drug that modulates glutamatergic neurotransmission in order to facilitate learning/memory.

Cholinesterase inhibitor — Drug that increases synaptic availability of acetylcholine via inhibition of cholinesterase enzymes.

Cognition — Mental function involving memory, language abilities, visual and spatial skills, intelligence, and reasoning.

Dentrites — Short, branching extensions of neurons that receive impulses from other neurons when stimulated by neurotransmitters released from presynaptic terminals.

Hippocampus — A seahorse-shaped temporal lobe structure of the brain that provides a model system for synaptic plasticity.

Long-term memory — Persistent record of experience that has been organized and rehearsed.

Mediation (of learning/memory) — Direct alteration in the specific substrate of learning/memory encoding, consolidation, or retrieval.

Modulation (of learning/memory) — Nonspecific, potentially bidirectional change in performance achieved indirectly by altering the strength or expression of a separate and independent learning/memory mechanism.

Nutraceutical — Natural dietary supplements not regulated by the Food and Drug Administration that are purported to sharpen mental functions and counteract the aging process.

Short-term memory — Transient record of experience lasting only a few seconds/minutes.

U-shaped curve — Hyperbolic line plot of drug dose/stimulus intensity relative to treatment efficacy reveals zeniths at low- and high-dose/intensity extremes and an intermediate nadir to form the shape of the letter U.

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