Modulation of memory storage

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For several decades, the concept of modulation of memory storage has significantly influenced research investigating neurobiological memory mechanisms. New evidence provides additional support for the view that stress hormones released during emotionally arousing situations modulate memory processes. Recent experiments have investigated the role of sympathetic adrenomedullary hormones in emotional memory in humans, as well as the role of adrenocortical hormones, primarily in animal studies. Further, it is becoming increasingly clear that the sympathetic adrenomedullary and the pituitary adrenocortical systems interact to modulate memory storage. Other new evidence emphasizes the role of peripheral influences to the brain on emotional memory, as well as the critical contribution of the amygdaloid complex in modulation of memory by emotional arousal.

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Abbreviations
APV 2-amino-5-phosphonovalerate
GABA γ-aminobutyric acid
NMDA *N*-methyl-D-aspartate

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Introduction

Not all memories are retained equally well. This fact makes sense from an evolutionary and functional perspective because animals, including humans, would appear to benefit little from having memories for trivial events that are as strong as memories for more important events. Thus, it makes sense that the brain should have evolved mechanisms for storing information that reflect the degree to which the information is worth storing. Systems that regulate information storage are clearly as important to an organisms' survival as are those neural mechanisms that store the information.

The concept of modulation of memory storage has guided extensive research into brain mechanisms of learning and memory over the past 30 years. This review highlights some of the more important recent developments in this research area, and focuses on those systems that appear to be most critical for memory modulation, namely, endogenous stress hormones released during emotional learning situations and the amygdaloid complex.

The concept of a memory modulatory system

The concept of memory storage modulation grew especially from three related discoveries. First, recently formed memories are susceptible to post-learning influences (e.g. drug injections, brain stimulation) for a limited time after they are formed [1]. Second, many post-learning treatments have the potential to either enhance or impair ('modulate') memory, depending on the experimental conditions [2]. Finally, some post-training treatments (e.g. injection of sympathetic stress hormones) affect memory storage even though they do not directly affect the brain [3–5]. From these facts, one may infer the existence of endogenous systems that influence memory storage processes but do not serve as the neural bases of memory storage. Compelling evidence that nervous systems contain memory-modulatory mechanisms came from work on invertebrate preparations (for discussion, see [6]).

There are several important characteristics of a memory storage modulatory system [7,8]. Perhaps most critically, the role of a memory modulatory system is time limited: with the passage of sufficient time, a modulatory system can be inactivated with no loss of retrieval of stored memories. Furthermore, such a system can either enhance or impair memory, depending on the learning conditions. Lastly, whereas memory storage mechanisms may serve only specific forms of memory, a memory modulatory system should be capable of influencing different forms of memory. These conclusions and implications are strongly supported by recent findings.

Stress hormones I: catecholamines

Modulation of memory storage has been most extensively studied in experiments examining the effects of catecholamine stress hormones. A very large body of evidence from animal studies indicates that adrenergic stress hormones released peripherally during emotionally arousing events modulate the storage of memory for the events [9,10].

The findings of two recent studies investigating the role of catecholamines in memory in humans are consistent with the findings of research with animals. In both studies, the enhancing effects of arousal on memory were impaired by β-adrenergic blocking drugs. Cahill *et al.* [11••] studied the effect, in healthy volunteers, of the β-blocker propranolol on long-term (1 week) memory for either an emotionally neutral story or a closely matched, but more emotionally arousing story. The drug selectively impaired memory for the emotionally arousing story. The effect of the drug could not be attributed to effects on attention or sedation, nor could it be attributed to a reduction of the emotional reaction of the subjects to the story. The findings support

the view that modulation of memory by emotional arousal depends on the activation of β-adrenergic receptors, even though such activation is not critical for normal memory under non-emotionally arousing circumstances.

A second study by Nielson and Jensen [12••], employing physically induced arousal (muscle tension) to enhance memory for written material, reported that young subjects, healthy elderly subjects, and elderly hypertensive subjects taking non-β-blocker medications all showed enhanced retention performance resulting from the arousal manipulation. In contrast, elderly hypertensive subjects taking β-blocker medication showed no evidence of enhanced retention with arousal. Although this study differs from that of Cahill *et al.* [11••] in several key respects (e.g. very different retention intervals, chronic versus acute dosing), both studies support the general conclusion that the enhancing influence of arousal (either emotionally or physically induced) on memory depends on β-adrenergic receptor activation. As noted above, these findings are consistent with studies examining the role of adrenergic activation in memory in animals.

Other recent work implicates the dopamine system of the prefrontal cortex in modulating memory storage. Recording from single neurons in the prefrontal cortex of monkeys performing a short-term memory task, Williams and Goldman-Rakic [13••] found that the spatially defined 'memory fields' of the cells were modified by iontophoretic application of antagonists to D1 dopamine receptors. More specifically, D1 antagonists increased the size of these 'memory fields', implying that D1 receptors modulate short-term (and possibly long-term) mnemonic processing. This same group has reported effects of D1 agonists and antagonists on short-term memory in monkeys [14]. An interesting related study reported that lesions of the central amygdaloid nucleus attenuated a stress-induced increase in dopamine turnover in the prefrontal cortex [15]. Considered together, these studies suggest that the effect of stress on memory may depend on amygdala influences on D1-related activity of the prefrontal cortex.

Glucose and memory

Epinephrine is the stress hormone most extensively implicated to date in memory modulation. In recent years, considerable evidence has suggested that epinephrine may affect memory, at least in part, via its well established effects on blood glucose levels. For example, when administered systemically after training, both epinephrine and glucose induce inverted-U, dose-response enhancement of memory [16,17]. Glucose has also been shown to enhance memory in elderly humans and in Alzheimer's disease patients [18,19].

Recent work has focused on the mechanisms by which glucose affects memory. The findings of Kopf and Baratti [20] support the view that the effects of glucose on memory depend on a central cholinergic mechanism. They found that central, but not peripheral, cholinergic manipulations interact with glucose to affect memory: sub-effective doses of centrally acting cholinergic antagonists impair, and agonists augment, the action of glucose on memory. Related to this, Gold and his colleagues [21•] found that both systemic and intra-septal injections of glucose augment the release of acetylcholine in the hippocampus. It is of particular interest that systemic glucose injections augmented hippocampal acetylcholine release only in a training situation that normally induces acetylcholine release [21•].

The role of glucose in modulating memory storage is probably specific to learning situations in which epinephrine is released. However, emotional arousal can influence memory in the apparent absence of epinephrine release as, for example, in situations where emotion reduces heart rate [22]. Thus, in emotionally arousing situations in which epinephrine is not released, it seems likely that β-adrenergic receptor activation (by norepinephrine) may be critical to memory enhancement [11••]. Because epinephrine is not released in such situations, glucose levels are not increased and, thus, are not likely to influence memory storage.

Stress hormones II: corticosteroids

In addition to inducing the release of adrenomedullary hormones epinephrine and norepinephrine, emotionally stressful events also release adrenocortical hormones. Unlike adrenomedullary stress hormones, adrenocortical hormones readily enter the brain [23]. It is also well established that corticosterone (the principle adrenocortical hormone in the rat) acts at two distinct receptors, the mineralocorticoid (or type I) receptor and the glucocorticoid (type II) receptor [24]. Most recent work into the effects of adrenocortical hormones on memory has focused on the impairing effects of high, sustained doses of these hormones (produced by multiple injections or chronic stress). For example, Newcomer *et al.* [25] found that four-day treatment of human subjects with dexamethasone impaired memory. In another study, Bodnoff *et al.* [26] reported that chronic corticosterone or stress treatment impaired learning of 'mid-age' rats in a water maze task.

The 'inverted-U' relationship between dose and retention performance is a well established outcome in studies of drug and hormone action on memory. The recent demonstrations of an inverted-U relationship between corticosterone levels and electrophysiological activity in the hippocampus thought to be related to learning [27,28] suggest that corticosteroid treatments should enhance performance under appropriate conditions, such as in studies using lower doses of corticosterone agonists. This implication has been supported by findings of several recent experiments [29••,30••]: injections of low doses of the synthetic corticoid dexamethasone enhanced retention of one-trial avoidance learning and attenuated deficits in water-maze learning produced by adrenalectomy [29••].

Because dexamethasone at this dose acts primarily at the glucocorticoid receptor, these results indicate that activation of the glucocorticoid receptor (which occurs primarily during periods of stress-induced elevations of corticosterone concentration) underlies the observed memory enhancement. How these findings relate to the currently more widespread view that glucocorticoid receptor activation (typically chronic) is related to impaired cognitive functioning (see [23]) remains to be determined. It seems likely that glucocorticoid receptor activation may induce either memory enhancement or memory impairment, depending on the degree of receptor activation, as well as interactions between glucocorticoid and mineralocorticoid receptors [24,31••]. Neuronal death (most studied in the hippocampus) probably underlies the memory impairment produced by chronic corticosterone treatments [32,33].

Recent findings indicate that adrenocortical suppression blocks the memory enhancing effects of epinephrine and amphetamine [34]. These findings are consistent with considerable earlier evidence indicating that adrenomedullary and adrenocortical systems interact during stressful learning situations to modulate memory: the effects of adrenomedullary hormones depend on the levels of adrenocortical hormones [31••]. However, the specific nature of this interaction remains controversial [24,31••].

Other modulatory influences

Many other neuromodulatory substances are released in response to stress, including β-endorphin, vasopressin, adrenocorticotropic hormone, substance P, and cholecystokinin. The findings of research investigating the effects of these hormones on memory are summarized in several reviews [10,31••,35,36•].

Evidence of peripheral nervous system modulation of memory

Considerable evidence indicates that memory modulation is initiated by influences from the PNS to the CNS. Most fundamental to this conclusion is the fact that many of the peptide and catecholamine hormones implicated in memory modulation do not readily pass the blood-brain barrier. An early indication of the importance of peripheral influences on memory came from the finding that peripheral, but not central, injections of the β-blocker propranolol attenuated the amnesia produced by stimulation of the frontal cortex [37]. More recent evidence indicates that the effect of epinephrine on memory is blocked by sotalol, a peripherally acting β-adrenergic antagonist [4].

A number of studies have suggested that afferents of the vagus nerve mediate the memory-modulating effects of peripherally administered drugs and hormones [38,39]. A recent study reported that direct electrical stimulation of the vagus can modulate memory storage. Clark *et al.* [40•] implanted rats with a cuff through which the vagus nerve could be stimulated. Stimulation of the vagus immediately after one-trial avoidance learning enhanced subsequent retention, and, in an important parallel to drug and hormone studies, the stimulus intensity effect on memory had an inverted-U relationship. Memory enhancement induced by epinephrine is also blocked by injections of a local anesthetic into the nucleus of the solitary tract, the brain stem region to which the vagus nerve projects [41].

Modulation of memory in the brain: sites of action of peripheral influences

Amygdaloid complex

The amygdaloid complex is the brain region most clearly implicated to date in the modulatory effects of peripheral drugs and hormones on memory. It has long been known that direct stimulation of the amygdaloid complex can modulate (enhance or impair) memory, and that the effects of amygdaloid complex stimulation on memory depend on the integrity of adrenal hormones [42,43]. Recent evidence from humans with selective amygdaloid complex lesions indicates that the effects of emotional arousal on conscious memory depend on the amygdaloid complex [44,45•,46•].

A consistent body of evidence from animal studies indicates that lesions of the amygdaloid complex or the stria terminalis, a major amygdaloid complex afferent–efferent pathway, block the effects of many drugs and hormones on memory [8]. This is true not only for memory enhancing agents, but for amnestic agents as well. Several recent studies have confirmed this view. Consistent with much earlier work, Roozendaal and McGaugh [29••] reported that the memory-modulatory effects of glucocorticoids depend on an intact stria terminalis, and on the integrity of the basolateral nucleus of the amygdaloid complex [30••]. However, lesions of the central amygdaloid complex nucleus did not block glucocorticoid-induced memory enhancement [30••]. Flood and colleagues [47] reported that the memory-enhancing effects of both epinephrine and the gut peptide cholecystokinin depend on an intact stria terminalis. However, they also reported that stria terminalis lesions did not block memory enhancement produced by the cholinergic agonist arecoline, suggesting that the effect of this drug on memory does not critically depend on the integrity of the amygdaloid complex. This finding conflicts with earlier evidence indicating that stria terminalis lesions attenuate the effects of the cholinergic drugs atropine and oxotremorine on memory [48].

As described earlier, two important criteria for a memory-modulatory system are, first, a time-limited involvement in memory, and second, an ability to influence different forms of memory. A recent report by Packard, Cahill, and McGaugh [49••] suggests the functioning of the amygdaloid complex in learning and memory satisfies both criteria. Rats were trained in either a spatial (hidden-platform) or cued (visible platform) water maze task. Earlier studies had demonstrated a double dissociation between the hippocampus and the caudate nucleus in the effects of both lesions and injections of dopamine

agonists on the learning of these two tasks. In this experiment [49••], rats received unilateral injections of D-amphetamine into either the hippocampus, the caudate nucleus, or the amygdaloid complex immediately after training in one of the two tasks. Retention of the tasks was tested one day later. As expected, D-amphetamine injection into the hippocampus enhanced retention of the spatial, but not cued tasks. Conversely, D-amphetamine injection into the caudate nucleus enhanced retention of the cued, but not spatial tasks. In contrast, D-amphetamine injection into the amygdaloid complex enhanced retention of both tasks. Furthermore, the enhanced retention produced by post-training D-amphetamine injection into the amygdaloid complex was not affected by inactivation of the amygdaloid complex (via infusions of lidocaine) immediately before the retention test. This finding suggests that locus of change underlying enhanced memory after amygdaloid complex stimulation is not within the amygdaloid complex. Packard *et al.* [49••] thus suggest that amygdaloid complex stimulation probably enhances memory in spatial and cued water maze tasks by influencing memory processes mediated by the hippocampus and caudate nucleus, respectively.

Evidence supporting this view comes from recent experiments (using c-Fos immunochemistry) showing that amygdaloid complex stimulation can functionally affect both the hippocampus and caudate nucleus (L Cahill, unpublished data; [8]), both of which have been implicated in some forms of memory [49••,50]. Ikegaya and colleagues [51,52•] have also recently shown that normal hippocampal long-term potentiation depends on influences from the basolateral amygdaloid complex. They report that both reversible [51] and permanent [52•] lesions of the basolateral amygdaloid complex nucleus attenuate the induction of long-term potentiation in the dentate gyrus *in vivo*. Collectively, the studies just described support the view that the amygdaloid complex modulates memory processes in other brain regions, especially the hippocampus.

Recent research has further implicated the amygdaloid complex in the modulation of memory storage by benzodiazepines (e.g. valium). The well established ability of these compounds to impair memory consolidation acquires heightened importance given the growing body of evidence for the existence of endogenous benzodiazepines [53]. The basolateral, but not central, amygdaloid complex nucleus has been implicated in benzodiazepine-induced amnesia [54]. A recent report supports this view: diazepam (i.e. valium) causes amnesia in rats for inhibitory avoidance learning when injected into the basolateral, but not central amygdaloid complex nucleus [55•]. Injection of another benzodiazepine, midazolam, into the basolateral amygdala also impairs conditioned avoidance responding and conditioned hypoalgesia [56]. Amygdaloid complex dependent mechanisms are further implicated in memory modulation by benzodiazepines by the recent observation that intra-amygdaloid complex injections of the GABAergic antagonist bicuculline block the amnesia induced by systemically administered midazolam [57].

Finally, recent research further implicates NMDA-dependent mechanisms within the amygdaloid complex in memory modulation. Liang, Hon, and Davis [58••] found that antagonism of NMDA receptors within the amygdaloid complex (with APV) produces a dose- and time-dependent retrograde amnesia for one-trial avoidance learning, but exerts no effect on retrieval of this task once learned. NMDA receptor blockade within the amygdaloid complex has also recently been shown to impair aversively motivated taste-potentiated odor conditioning [59].

The septo-hippocampal system

Although the amygdaloid complex is the brain region most implicated to date in drug and hormone modulation of memory, other brain regions, including the septo-hippocampal system also appear to be involved. The time-limited involvement of the septo-hippocampal system in long-term memory is well established [60•,61,62], and is consistent with a memory-modulatory role. Also, the septo-hippocampal system possesses a high number of receptors for many known memory-modulating agents, such as corticosterone (discussed earlier) and benzodiazepines [63]. Indeed, a recent report suggests that the septo-hippocampal system is involved in benzodiazepine modulation of spatial memory: injection of the benzodiazepine chlordiazepoxide into the medial septum impaired working memory in a radial arm maze task [64]. In addition, both GABAergic [65,66] and opiatergic [67] dependent mechanisms in the septo-hippocampal system appear to be important in regulating long-term memory storage in a several learning situations. Each of these experiments is consistent with a modulatory role for the hippocampus in long-term memory storage.

Conclusions

The concept of memory modulation continues to guide research into the neurobiology of memory. This research is helping to reveal how emotional arousal affects long-term memory storage in both animal and human studies. Recent research has reinforced the evidence that two factors, at minimum, are critical to the effects of emotion on memory: β-adrenergic activation (centrally and/or peripherally) and the amygdaloid complex. However, the evidence also suggests that complex interactions among many hormones and brain systems regulate the storage of long-term memory. Understanding these interactions is now a major goal of studies investigating the modulation of memory storage.

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