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THE PHARMACOLOGY OF MEMORY: A NEUROBIOLOGICAL PERSPECTIVE[1,2]

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INTRODUCTION

What is of interest in an area of scientific inquiry depends on one's perspective. If one looks primarily to find a drug that can improve memory in the healthy subject or retard the decline of memory in neurological disease, then any enhancing effect of a drug can hold promise. Further, a better memory test score occurring together with a wide spectrum of other drug actions might mean only that memory enhancement will inevitably be accompanied by side effects. Alternatively, if one wishes to know how the brain accomplishes memory storage, then drugs can be viewed as tools to dissect the neural machinery involved in memory and to reveal as much as possible about the neurotransmitter systems and biochemical steps involved. Drugs may also be viewed as tools to reveal structural principles of memory, such as how memory changes over time and how many processes are involved.

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In this way something might be learned about its relationship to other functions, and about the nature and organization of brain systems participating in the formation, development, and expression of memory. From this perspective, the wider the range of a drug's effects on behavior, the less its usefulness; and it is of first importance to understand whether a change in performance reflects a change in memory storage itself, a change in a biologically significant system that influences memory, or a change entirely unrelated to memory that appears only because the drug under study happens to affect a particular measure of performance.

Although the literature of pharmacological studies of memory belongs to all these worlds, the orientation of this review is primarily neurobiological. We do not catalog all pharmacological treatments known to affect learning or memory. Instead we focus on acetylcholine, macromolecules, peptides, and the catecholamines, since there appear to be principled reasons for linking these substances to memory. In addition, where possible we draw together from the literature information about neural mechanism and biological organization. Finally, when basic research has led to clinico-pharmacological studies in normal human subjects or patients, we attempt to summarize that work.

The pharmacological analysis of memory can best be understood in the context of a broader effort to appreciate the biochemical, neurophysiological, and anatomical events that subserve information storage, an effort that connects the study of memory to a large portion of the enterprise of neuroscience. The neurosciences are presently experiencing a rapid and exhilarating growth of technology, facts, and concepts. Phenomena as superficially dissimilar as collateral sprouting after brain injury, denervation supersensitivity, drug tolerance, and programs of morphological reorganization during development all reflect the brain's capacity for plasticity; many have suggested that such phenomena hold clues for understanding the instance of brain plasticity that we call memory.

This broad perspective has helped us learn a great deal about memory, and has provided a useful framework within which to consider pharmacological studies. Principal concepts that have guided neurobiological investigations of memory include a distinction between intrinsic and extrinsic neural systems (1), the concept of modulation (2–4), a distinction between short-term and long-term storage mechanisms (5–7), and the concept of consolidation (8, 9).

The distinction between intrinsic and extrinsic systems derives largely from cellular investigations of learning and memory in invertebrates. The intrinsic system refers to pathways wherein representations of information actually develop, presumably as a result of alterations in synaptic efficacy; the extrinsic system refers to pathways that can influence the development,

maintenance, or expression of memory, but which do not themselves contain the memory (1). Neurons are capable of history-dependent behavior, e.g. low frequency depression, which in some species is known to provide the synaptic basis for certain types of short-term information storage. In the case of habituation of gill withdrawal in *Aplysia,* for example, memory develops as synaptic changes along the same pathways that are hard-wired for performance of the response (10). If this principle is preserved in vertebrates, it would help us understand why it has been so difficult to localize memory storage (11). This would be the case because any disruption of activity in the intrinsic system would necessarily affect the ability to perform the response. In *Aplysia* an extrinsic system has also been identified which acts heterosynaptically on the habituated, intrinsic pathway and which is responsible for sensitization. Disruption of activity in the extrinsic system could in principle affect memory without affecting the ability to perform the hard-wired response.

The idea of an extrinsic system, which developed from invertebrate neurobiology, gives meaning to the related concept of *modulation.* There is now good biochemical and physiological reason to speak of this mode of neuronal interaction (2, 4). For example, neurohormones can act at a distance on target sites, over a time course far exceeding the millisecond range of classical neurotransmitters. In this way, neurohormones could modulate the more punctate local events reflected in conventional synaptic communication. At the behavioral level, the term modulation has a less precise meaning, but several behavioral examples of modulatory influence have been approached at the cellular level in invertebrates (2). In the case of learning and memory, it has seemed reasonable that brain events corresponding to processes like reinforcement should modulate the nature and strength of memory storage, since the value of information to an animal and whether or not information should be stored in memory depends in part on events that occur after it has been registered. Accordingly, it is of interest that a variety of treatments, some of which will be considered here, have been shown to affect retention when applied after initial training, in a way that suggests modulatory influences upon intrinsic, information-containing networks (3). Clearly, the pharmacology of memory extends beyond memory as we ordinarily speak of it, and must include functions like attention, reward, and arousal that will necessarily influence memory.

Short-term memory has been distinguished from long-term memory on various grounds, some more compelling than others. Among the reasons for supposing that long-term memory involves different neural mechanisms than short-term memory are (*a*) the possibility that the formation of long-term memory, but not initial learning or short-term memory, depends on de novo brain protein synthesis (12–14) and (*b*) the observation that

amnesic patients have difficulty acquiring new memories, despite an intact ability to perform digit-span tasks and to hold information for a short time (15–17). The development of long-term memory appears to occur over a period of time and might involve biochemical events that alter synaptic connectivity in a stable way, or morphological changes in the topography of synaptic connectivity. A variety of such changes have been correlated with behavior (13, 18, 19), but none of these has yet been clearly linked to behavioral memory.

The fact that long-term memory develops over time has sometimes been called the consolidation process. In large part, this notion is based on the finding that memory disruption by post-training treatment is less effective the longer the interval between training and treatment. It is worth mentioning that there is some ambiguity surrounding current use of the term consolidation. The maximum interval after training when memory disruption can occur varies widely, depending on the experimental situation (seconds to hours in experimental animals, years in humans). For example, work with amnesic patients has suggested that long-term memory continues to change for years after learning, and that the time course of these changes may depend on the time course of normal forgetting (20). A similar idea has been proposed to account for the effects of cholinergic drugs on memory in the rat during the weeks after learning (21). Thus, some now refer to consolidation as the process by which resistance to disruption develops gradually after training. By this usage consolidation involves long-term memory and can continue for years. Others refer to consolidation as the relatively short-lived process of transition from a labile short-term storage system to a viable long-term storage system, knowing that the time period after training during which memory can be disrupted need not reveal the time course of consolidation.

In the review that follows, the effects of drugs on memory are considered. Where possible the results are related to our emerging understanding of the neurobiology of memory, as just briefly outlined.

ACETYLCHOLINE

An extensive literature on the effects of drugs that alter the efficacy of brain acetylcholine (ACh) suggests that cholinergic synapses may be part of the intrinsic system that accomplishes memory storage. This idea is based largely on the effects of cholinesterases and anticholinergic drugs on memory for previously learned tasks (21, 22). For rats trained in appetitively or aversively motivated tasks, the anticholinesterases physostigmine or diisopropylfluorophosphate (DFP) given prior to retention testing had no effect,

impaired performance, or facilitated performance, depending on the age of the memory at the time of treatment. The anticholinergic scopolamine had opposite effects at each training-retention interval. For example, intracerebral injection of 0.02 ml of 0.1% DFP had no effect on a 1- or 4-day old discrimination habit, impaired memory of a 7-day-old habit, and facilitated memory 21 days after learning at a time when normal animals exhibited forgetting. Since the same dose of drug impaired or facilitated performance depending on the training-retention interval, it is possible to rule out the influence of some side effect of the drug on performance. The same point follows from the observation that a given dose of physostigmine can facilitate retention of a poorly learned habit while impairing retention of a well-learned habit (23).

These results have been taken to mean that memory storage involves, in part, a sequence of changes in efficacy at cholinergic synapses that develop with time after learning (22). For a task that can be remembered for weeks, these changes are thought to involve first a gradual increase in efficacy of cholinergic transmission for several days after learning, and then a gradual decrease in efficacy during the course of forgetting. When physostigmine is given several days after learning, it is presumed to raise the efficacy of cholinergic transmission above the optimal level, which has already been achieved, and to impair performance. During normal forgetting, physostigmine is presumed to raise the efficacy of transmission to an optimal level that permits recall.

Recently this body of work has been replicated and expanded (24). In keeping with the idea contained in the basic hypothesis (21), the effects of cholinesterase treatment depend not only on drug dose and age of the memory, but also on the efficiency of original learning. Specifically, during the days after learning, slow learners responded to physostigmine differently than fast learners. It has been suggested that the hypothesized sequence of synaptic changes subserving memory storage occur more rapidly for the fast learners, so that this group achieves the stage of retention that can be disrupted by physostigmine sooner than slow learners. Taken together, the evidence strongly suggests that synaptic changes occur gradually after learning and that their time course is related to the natural lifetime of the memory.

This idea is strongly supported by recent studies of human amnesia (20, 25) that have confirmed the long-standing clinical observation that retrograde amnesia can affect memories formed a few years previously without affecting older memories (26). These findings have suggested that memory changes gradually during the years after learning so as to become more resistant to disruption. Since forgetting also occurs during the years after

learning, considerable reorganization may take place within long-term memory such that some information is lost while other information becomes more resistant to disruption.

The evidence reviewed here is consistent with the hypothesis that memory storage involves a gradually developing program of events, including changes in the ability of cholinergic synapses to transmit information. Because effects of these drugs can apparently be obtained throughout the lifetime of a memory, and because these effects reveal properties of the memory storage process, it seems reasonable to localize these hypothetical synaptic changes to the intrinsic system, i.e. to the ensemble of neurons actually storing information.

If the intrinsic system for information storage involves the same neuronal systems required for performing the task that is to be remembered (13), then it follows that cholinergic drugs should not produce pure amnesia but instead should produce a state of cognitive impairment that includes amnesia. This expectation seems borne out by studies of adult humans (27, 28) and monkeys (29) showing that scopolamine produces a broad impairment in cognitive functions including memory, which resembles the pattern of cognitive deficits observed in aging.

Despite this convergence of supporting data, the idea that cholinergic synapses store memory still rests on indirect evidence. Techniques are not yet available to determine directly either the synaptic basis of long-term memory storage or the neurotransmitters involved. It remains possible that cholinergic drugs are exerting their effects via cholinergic neurons upon crucial noncholinergic systems. In this regard it would be of interest to discover whether any other synaptically active drugs can exert effects on memory which vary across the lifetime of the memory as a function of its age.

In any case, the fact that the effects of cholinergic drugs are dependent on age of the memory, the drug dose, and learning efficiency has clear implications for the development of treatments for memory disorders in humans that might involve the cholinergic system. Efforts to develop such treatments are considered next.

Memory Disorders and Cholinergic Drugs

Since the discovery of the role of dopaminergic neurons in Parkinson's disease and the development of L-dopa for its treatment, there has been interest in the possibility that other neurological disorders might be discovered to affect one transmitter system disproportionately, and that such disorders might respond to treatment with appropriate agonists. Recently, it has been suggested that Alzheimer's disease, the most common form of senile dementia, might selectively involve cholinergic neurons at least in its

early stages. In one study of three patients with Alzheimer's disease, choline acetyltransferase (CAT) was reduced in cortex by more than 80% without measurable losses of glutamic acid decarboxylase, tyrosine hydroxylase, dopamine-β-hydroxylase, monoamine oxidase, and aromatic amino acid decarboxylase (30). Reduction of both CAT and acetylcholinesterase activity, but not glutamic acid decarboxylase activity, appeared to correlate with neuropathological criteria for dementia of the Alzheimer type (e.g. plaque formation in cerebral cortex) and with intellectual impairment (31). It has also been reported that reductions in CAT can occur without commensurate losses in muscarinic cholinergic receptor binding activity (31–33). It seems possible that this pattern of loss could reflect an early stage of the disease prior to gross neuronal loss. Alternatively, as suggested previously (32), the pattern of loss observed could correspond to loss of cholinergic neurons and denervation supersensitivity. In either case, these findings raise the possibility that Alzheimer's disease selectively affects cholinergic neurons, and provide a rationale for asking whether regimens of cholinergic drugs might retard the decline of cognitive function associated with this disease.

Large-scale, well-designed studies of cholinergic drugs and Alzheimer's disease have not yet been accomplished. Preliminary results have been reported for three patients who reportedly improved on a picture recognition task after an injection of 0.125, 0.25, or 0.5 mg physostigmine (34). Test doses were individually selected after screening all three doses on separate days. It has also been reported that physostigmine (1.0 mg) had no effect on memory in a "moderately demented" patient with Alzheimer's disease (35). In view of the study just described, this case report using one dose is not particularly informative, especially since 1 mg may be too high a dose. In another preliminary report five patients with Alzheimer's disease received either physostigmine (0.005–0.015 mg/kg) or lecithin (12 g orally three times daily), or both treatments together (36). Lecithin is the major source of choline in the normal diet, and its ingestion increases ACh concentrations in rat brain (37). No consistent pattern of results emerged, though three patients given both drugs improved their performance on a memory test compared to their performance when on lecithin alone. It was not clear why these same effects were not evident when the results with both drugs were instead compared to placebo, or why lecithin and physostigmine given alone impaired the performance of two out of five patients.

The effects of separate treatment with lecithin or choline has also been examined. Seven early-stage Alzheimer patients received daily incrementing doses of lecithin for 4 weeks, reaching an average dose of approximately 75 g per day (38). Three of the patients improved their scores in a test of new learning ability, without changes in immediate memory, remote mem-

ory, or other cognitive skills. Choline (9 g daily for 21 days) improved memory test performance to a small extent in three patients identified as exhibiting early-stage Alzheimer's disease, but did not affect the test scores of patients with more advanced stages of the disease (39). This study did not include a placebo group. Finally, three other studies of choline involving 3 to 18 patients found no changes in mental status following one to two months of daily choline treatment (8 g to 15 g) (40–42). Taken together the available studies have been largely disappointing. The small number of patients studied, lax experimental designs, inadequate attention to dosage, and the lumping together of results from early-stage and late-stage patients have made it difficult to draw any firm conclusions about the possible usefulness of cholinergic drugs in dementia.

It is worth noting, however, that which drugs will be useful in Alzheimer's disease will depend on the specific nature of the neuropathology. If this disease markedly reduces CAT activity without affecting muscarinic binding activity, then little benefit can be expected from physostigmine, which would require release of ACh for its cholinesterase-binding action to be useful; and little benefit might be expected from choline, which requires CAT in order to be converted to acetylcholine. Recently, however, choline has been shown to excite ACh responsive cortical neurons by a direct action (43); hence, large doses of choline might conceivably exert postsynaptic effects in the absence of presynaptic mechanisms for its uptake and conversion to ACh. In any case, cholinergic agonists like arecholine, which do not depend for their effects on intact presynaptic structure, would seem to be the best candidates.

Somewhat more is known about the effects of cholinergic drugs in normal adult subjects. Infusions of arecholine (4 mg) (44) or physostigmine (1.0 mg/hr) (45) facilitated word learning, and the effect was greater in poor learners. Arecholine (i.v. 2 mg) also facilitated word recall when the drug was given immediately after learning (46). A single oral dose of choline (10 g) improved serial learning in normal subjects (47). All these effects were small but reliable. Regimens of cholinergic drugs given over longer periods of time have been less effective. Thus choline chloride (16 g/day for 2 days) had no effect on memory test scores in normal elderly subjects (48), and no effect was observed in normal young adults, when the same dose was given for a three-day period (49).

In summarizing these data it is useful to keep in mind the elegant animal studies that first demonstrated that the effects of cholinergic drugs are largely determined by drug dose and by the age of the memory. Efforts to develop therapeutically useful applications of this work will no doubt be constrained by these two variables. First, as has been pointed out previously

(34), a therapeutically appropriate dose may have to be selected for each patient. Indeed, too high a dose (e.g. 3 mg physostigmine) can impair cognitive function (50). Second, useful memory improvement in normal subjects by cholinergic drugs seems unlikely, since doses that improve recall of some memories can be expected to impair recall of others. Finally, long-acting cholinomimetic substances will be needed. Cholinergic agonists that do not depend on the integrity of the presynaptic neuron would seem the most promising. Large, double-blind studies using standardized neuropsychological tests will be necessary to evaluate the possible usefulness of such drugs.

PROTEIN SYNTHESIS

Because of the importance of protein synthesis in cellular regulatory processes, it has long seemed reasonable that protein synthesis might be involved in memory in some way, and that protein synthesis could be one in a series of steps needed to form lasting alterations in synaptic efficacy along specific neuronal pathways (51). If this program of events results in morphological changes at synapses, then protein synthesis might continue to be involved in the maintenance of memory as the constituent elements of the synaptic region are degraded and replaced.

In the literature of the pharmacology of memory, studies using drugs designed to specify the role of brain protein synthesis in memory are perhaps the most prevalent. No attempt is made to present all this work here, since several recent reviews are available (12, 18, 52, 52a). The results can be summarized by stating the basic findings. When cerebral protein synthesis is inhibited by 90–95% just before or after training in a simple task, initial learning is normal but amnesia develops gradually and is present within a few hours. When inhibition is established 30 min or longer after training or just prior to retention testing, memory is not affected. These observations have been obtained in rodents, birds, and fish in a wide variety of tasks, using three classes of drugs that inhibit protein synthesis by different mechanisms of action. The results have generally been taken to mean that brain protein synthesis during or shortly after training is required for the formation of long-term memory. In addition, the long-term memory process that is dependent on protein synthesis appears not only to be established within minutes after training, but also to be necessary shortly after training for the full expression of memory. When training occurs during a period of brain protein synthesis inhibition, performance declines gradually in the hours after training and marked amnesia is observed in retention tests conducted after this time. It seems reasonable to suppose that

protein synthesis related to formation of long-term memory takes place in the intrinsic system, in neurons that participate directly in information storage.

Protein synthesis may be involved in part in establishing persisting patterns of neuronal connectivity at cholinergic synapses. A transient increase in muscarinic cholinergic receptor binding occurs in the forebrain of chicks shortly after passive avoidance learning (57). This effect can be blocked by inhibitors of protein synthesis, so the change in binding may also be part of the information-containing intrinsic system. Other processes that operate during or shortly after initial learning may modulate the developing patterns of connectivity through extrinsic systems. It therefore seems unfruitful to search for a common mechanism underlying experimental amnesia (58, 59). Protein synthesis is presumably only one of several steps required to establish an intrinsic system, and other extrinsic processes may modulate this system.

These ideas about the role of protein synthesis in the formation of long-term memory lead naturally to expectations about the structure and time course of short-term memory. For example, it has been suggested that a short-term, information-holding mechanism is needed which is independent of protein synthesis, and which can last for at least a minute or two during the time that would be required for synthesis and transport of protein (6). In *Aplysia,* just such a mechanism (e.g. the low frequency depression underlying short-term habituation) has been identified and is known to occur normally in the absence of protein-synthesizing capacity (53).

Whereas there is rather good agreement about the behavioral effects of drugs that inhibit protein synthesis, it has been more difficult to establish conclusively that these effects are due to inhibition of protein sysnthesis required for memory formation, and not some other pharmacological action of the drugs. Nevertheless, many known side effects of the inhibitors have been specifically dissociated from amnesia (54). In particular, the possibility that the drugs cause amnesia by disrupting catecholamine metabolism has been evaluated in several ways and seems unlikely (54–56). These demonstrations, of course, do not bear on the possibility that catecholaminergic systems or other transmitter systems might participate in memory formation in some way. Indeed, in the sections that follow, we suggest that a number of other systems probably influence the development of memory.

The hypothesis that protein synthesis is required for memory formation is also supported by studies demonstrating increased incorporation of nucleotides into RNA and of amino acids into protein during learning (18, 52, 60–62). In the case of imprinting in the chick, which has been particularly well studied, these changes occur primarily in the medial hyperstriatum ventrale (63, 64). When this region is destroyed, the imprinted response is

lost and cannot be reacquired, suggesting that this site might contain the neural machinery required to accomplish imprinting and might also be the site of storage of imprinted information. Thus, some incorporation studies appear to support the notion that protein synthesis related to memory occurs in the intrinsic, information-containing system. Yet, it seems unlikely that all instances where protein synthesis has been demonstrated by incorporation studies to correlate with learning reflect changes in the intrinsic system. In the case of float-training in the goldfish, for example, the proteins whose synthesis is related to successful learning appear to modulate memory by diffusion into the ventricles (61). It will be the task of subsequent work to specify the role that protein synthesis plays in intrinsic and/or extrinsic systems, what kinds of proteins are involved, and whether changes in protein synthesis provide a long-lasting regulatory mechanism that itself alters neuronal connectivity or whether protein synthesis is an obligatory step needed to achieve morphological changes in neuronal connectivity.

PEPTIDES

More than 20 peptides having potent biological activity have been identified in mammalian nervous system (65, 66). Based on several lines of evidence, many of these are believed to have functional significance in the central nervous system. They are widely distributed in the brain (66), their iontophoretic application affects neuronal excitability (67), and they can affect behavior (68). The fact that peptides and peptide fragments, essentially devoid of classical endocrine activity, can exert potent behavioral effects has led to suggestions that peptides are involved in the central control of some forms of adaptive behavior (69). Of the peptides reported to influence learning and memory (e.g. α-MSH, β-LPH, ACTH, vasopressin, endorphins, enkephalins, substance P, oxytocin), ACTH, vasopressin, and the opioid peptides are presently receiving the most attention.

ACTH

Three behavioral effects of ACTH and ACTH fragments in learning paradigms have been extensively investigated in rodents. First, when given just prior to testing, the whole molecule $ACTH_{1-39}$ or the fragment $ACTH_{4-10}$ increases resistance to extinction of aversively or appetitively motivated tasks; that is, it prolongs performance of a previously acquired behavior after reinforcement has been withdrawn (69, 70). Initial acquisition of the same task need not be affected by ACTH treatment (71, 72). Second, ACTH or ACTH fragments can restore the impaired acquisition of shock-avoidance learning exhibited by hypophysectomized animals (73). Third, when

given prior to retention testing these same substances can reportedly attenuate the retrograde amnesia caused by CO_2 or ECS (74). These particular effects of ACTH are believed to be independent of its classical endocrine action on the adrenal glands primarily because $ACTH_{4-10}$, which is virtually devoid of adrenocortical activity, exerts these same effects (68, 75).

Resistance to extinction has been analyzed rather carefully in other contexts (76). Changes in attention, arousal, or motivation can underlie variations in extinction rate, and it is not at all clear that this phenomenon should be taken as evidence that a drug exerts effects on memory. Moreover, it is widely recognized that whenever a drug is active during behavioral testing, it is difficult to separate effects on memory from effects on other aspects of brain function, and to exclude possibly trivial effects, e.g. changes in shock sensitivity or locomotor activity that can markedly affect the performance measure in some tasks (77).

The finding that the restorative effects of ACTH on acquisition performance of hypophysectomized animals are short-lived (78, 79) suggests that ACTH may not be influencing learning and memory, since effects on memory might be expected to endure beyond the acquisition phase. Similarly, the so-called anti-amnesic actions of ACTH and ACTH fragments are consistent with effects on arousal or on learning ability and without further analysis cannot be taken as evidence for improved memory. Apparent recovery from amnesia has been analyzed rather carefully in other situations (80, 81), so experimental methods for discovering the basis for recovery are available. For example, testing animals on the reversal of an originally trained discrimination can reveal whether a drug is improving access to a previously acquired memory or whether it is simply facilitating learning and performance in a general way.

Whereas these studies suggest to us that the presumed central effects of ACTH do not pertain to memory in any direct way, studies with rodents suggest that the peripheral endocrine effects of ACTH may initiate events needed for memory to develop. When injected after training, 3.0 IU ACTH facilitated retention of passive avoidance training with a low intensity footshock and impaired the retention of training with a high intensity footshock (82). These effects were time-dependent, largest for treatments immediately after training and smaller with increasing intervals between training and treatment.

These findings have led to a useful formulation that might help in understanding many of the effects of post-training treatments on memory (3). By this view hormones like ACTH are thought to mediate some of the physiological consequences of an experience, and brain events initiated by the action of such hormones are thought to influence whether information about an experience will be remembered. In the case of training with low

footshock, exogenous ACTH might amplify the normal physiological consequences of training to produce a brain state that is optimal for information storage. In the case of training with high footshock, exogenous ACTH is thought to amplify what may already be an optimal condition for information storage, and to disrupt retention, perhaps in the same way that too high a level of arousal can disrupt learned performance (83). Thus the role of ACTH is considered to be modulatory, and its action on memory storage is considered to occur via an extrinsic system that operates after information has been registered and that influences whether information should enter long-term storage. Although the available evidence suggests that this modulatory role of ACTH on memory is initiated by its peripheral endocrine action, this idea has not yet been tested directly by demonstrating positive effects of ACTH and negative effects of ACTH fragments in the same task. Two studies, one with $ACTH_{4-9}$ (84) and one with $ACTH_{4-10}$ (85), have reported negative results with the passive avoidance task, but one positive report for $ACTH_{4-10}$, within the same task, has also appeared (86). If hormonal responses to training are normally involved in modulating the storage of information, then treatments that block the release of these hormones should impair retention. In the case of ACTH, this expectation has been borne out by the finding that hypophysectomized rats do have poorer retention of passive avoidance training than normal rats (87).

ACTH: HUMAN STUDIES The available studies on human subjects given ACTH fragments are in agreement with the animal studies in that these substances do not seem to exert any direct effect on memory. This conclusion is based on failures to observe effects on memory in double-blind, controlled studies of normal volunteers given single infusions of 15–30 mg of $ACTH_{4-10}$ prior to tests of free recall (88), paired associate learning (89, 90), and short-term retention of verbal or nonverbal material (90, 91). ACTH-like peptides, however, do seem to affect performance on some tasks requiring detection or vigilance (89, 92). Although these effects have been taken to reflect improvement in attentional processes (93, 94), this possibility has not yet been explored in better-understood paradigms where attention in human subjects can be profitably investigated (95). It is also worth noting that ACTH-like peptides can sometimes impair performance on tasks that would appear to depend substantially on attentional skills. For example, when subjects were simultaneously presented with six digits aurally and six letters visually, $ACTH_{4-10}$ (30 mg) markedly impaired immediate recall (91).

Some efforts have also been made to discover clinical uses for ACTH-like peptides in individuals with cognitive impairment. In elderly, cognitively impaired patients, $ACTH_{4-10}$ (30 mg) impaired 24 hr retention of the mild-

ly impaired patients and improved 24 hr retention of the severely impaired patients. Simple visual reaction time was uniformly slowed (96). No effects of $ACTH_{4-10}$ (30 mg) were observed in a group of organically impaired elderly patients (97) or in geriatric patients complaining of memory loss (98). In summary, ACTH fragments do not appear to affect memory in man, and the nature of their effects remains unclear. It will be the task of subsequent work to determine whether these substances sometimes affect behavior simply by increasing cooperation or combating fatigue, or whether they have a more specific effect.

Vasopressin

Arginine-8-vasopressin (AVP), the naturally occurring neurohypophyseal peptide, and the related peptide lysine-8-vasopressin (LVP) appear to exert their behavioral effects by mechanisms unrelated to classical endocrine activity. This conclusion is based on the observation that desglycinamide-lyside-8-vasopressin (DGLVP), which is devoid of endocrine activity, shares the behavioral effects of AVP and LVP (69, 99).

In contrast to ACTH, vasopressin's effects on behavior appear to be relatively long-lasting. When given after training, LVP prolonged extinction for at least three days (100). Similarly, when given daily for seven days (1 mg/day subcutaneously) AVP improved shuttlebox avoidance learning of hypophysectomized rats and maintained performance at a stable level for up to seven days after the last injection (78). Post-training administration of AVP, LVP, or DGLVP facilitated long-term retention of passive avoidance training (101–105), and long-term retention of sexually motivated learning (106).

Since these effects were most marked with short training-treatment intervals, they might reflect some modulatory effect of vasopressin on memory that could operate for a short period after training. If so, then it should be expected that memory defects would occur in animals deficient in vasopressin. This expectation has been borne out by studies of neurohypophysectomized rats, homozygous rats of the Battleboro strain who have diabetes insipidus and lack vasopressin in the cerebrum, and rats treated intraventricularly with antiserum to AVP. In each of these conditions, using shuttlebox avoidance, pole-jump avoidance, or passive avoidance, acquisition or short-term retention can be normal but retention is abnormal 24 hr or longer after training (99, 107–110). At least in the case of antiserum to AVP, these defects depended on the loss of vasopressin activity in the central nervous system. Intravenous injection of sufficient antiserum to remove vasopressin from the peripheral circulation did not affect retention (111). Taken together, these studies suggest that central effects of vasopressin might normally play some role in the formation of memory. This conclu-

sion could be strengthened by demonstrations that its effects are truly specific, i.e. that other hormones do not share its effects. Whereas ACTH does not appear to act like vasopressin, there has apparently been little effort to develop a list of other hormones that do not exert vasopressin-like effects on behavior. In addition, it would be of considerable value to extend the behavioral analysis of these hormones beyond passive avoidance behavior and extinction measures to discrimination tasks or other situations that are not so easily contaminated by simple changes in locomotor activity or in the general health of the animal.

VASOPRESSIN: HUMAN STUDIES Recently, the body of behavioral work with vasopressin and experimental animals has been extended to human subjects. In four amnesic patients (1 alcoholic, 3 post-traumatic), an uncontrolled trial of vasopressin nasal spray was said to improve memory and mood (112), but no neuropsychological testing was done. Two alcoholic Korsakoff patients treated with 16 IU vasopressin daily for two to three weeks exhibited no change in their condition, as judged by unspecified psychometric tests (113), but one patient given 22.5 IU daily for two weeks appeared to improve his scores on tests of new learning ability and on the digit-symbol substitution task, a nonmemory task which is sensitive to the cognitive defects associated with Korsakoff's disease (114). In a double-blind study, 12 neurologically intact patients aged 50–65 were assigned a daily regimen of 16 IU of vasopressin nasal spray for three days, and compared to 11 patients assigned placebo. Treated subjects appeared to perform better on some tests of memory, and also on tests of perceptual-motor speed and attention (115). Finally, four depressed patients treated with a long-acting synthetic analogue of vasopressin (1-desamino-8-*d*-arginine vasopressin) exhibited improvement of memory test scores, possibly secondary to improved effect (116). Since vasopressin improved performance on tests requiring speed along with memory test scores, it is presently unclear whether its effects should be linked to memory in a direct way, or whether vasopressin might be acting indirectly on memory by improving mood, attentiveness, or some other aspect of performance. Recently, vasopressin has been proposed to have a role in the pathophysiology of affective illness (117). If vasopressin influences mood or arousal, it might be part of a system that signals the importance of immediately preceding events. Other biological systems have also been proposed to participate in such a modulatory process (3, 118, 119).

Opioid Peptides

There has recently been great interest in both the enkephalins (methionine-enkephalin and leucine-enkephalin) and the endorphins (α-endorphin, β-

endorphin, γ-endorphin, and C' fragment) because they bind specifically with brain receptors previously known to interact with opiate analgesic drugs (120). They can also produce profound behavioral effects when injected intracerebrally in relatively small amounts (121). Only a few studies have assessed possible effects of opioid peptides on learning and memory. For aversively motivated tasks, subcutaneous or intracerebral injections of enkephalins, endorphins, or other opiate agonists shortly after training impaired later retention (122–127). Since naloxone could block this impairment, opiate receptors would seem to be involved in these behavioral effects in some way. Naloxone given alone facilitated retention. Contrary reports that opioid peptides can facilitate performance in aversive tasks are difficult to evaluate because of the high dose employed [intraventricular injection of 10^3 X the amount of whole brain met-enkephalin (128)], or because the drug was active during behavioral assessment (129). For appetitive tasks, peripheral injection of met-enkephalin or an analogue facilitated acquisition of maze learning in rats and discrimination reversal learning in monkeys (130, 131).

It has been suggested that the opioid peptides might impair retention of aversively motivated tasks because they attentuate the fear (132) or aversiveness (133) associated with pain. If so, this presumably does not reflect a direct reduction of pain sensitivity, since the reported behavioral effects occur at doses lower than those needed to produce analgesic effects (129, 134). The results with appetitive tasks appear to require some different explanation. However, if appetitive and aversive tasks do turn out to be affected in consistently opposite ways by opioid peptides, as the results so far available suggest, then it would be difficult to attribute the effects of these peptides to changes in memory storage processes. Perhaps their action depends instead on shifts in reward value or affect. The impact of such effects on performance would be expected to vary depending on the nature of the task.

Another way of thinking about the behavioral effects of opioid peptides and naloxone comes from studies suggesting that they alter selective attention (135, 136). Thus, in rats naloxone affected exploratory activity so as to increase the time spent in contact with stimuli, and morphine had the opposite effect (136). Preliminary results with event-related evoked potentials in human subjects also suggest that naxolone might enhance selective attention. Naloxone has been found to increase the amplitude of the N100 wave in a dichotic listening task designed specifically to evaluate selective attention (A. Arnsten, personal communication).

If the opioid peptides decrease sensitivity to aversive events or decrease attention, then it is understandable how they might affect memory at least in some situations. Sensitivity to fear or attention, however, would seem to

be more relevant at the time of learning than during the 30 min or more after learning when treatment with opioid peptides can affect subsequent retention. The finding that drugs can affect memory when given after learning has often been taken to reveal modulatory processes involved in the formation of memory (3). Perhaps some physiological processes, initially evolved to operate at the time of stimulus and response so as to modulate an organism's perception or direct its attention, also came to operate during the important period after an event has been perceived when its consequences determine whether it should be remembered. By this view many of the same processes involved in perception, attention, or response at the time an event is first experienced may also be involved in the post-training modulation of memory storage.

In considering the results of studies in which post-training drug treatment impairs retention, another possibility might also be considered. If memory formation requires the orchestration of several different physiological events during the time after training, then the disruption of *any* important brain process shortly after training might disrupt retention, even if the disrupted process ordinarily played no direct role in memory formation. If this were the case, then the familiar, post-training disruption effect might not in itself constitute a satisfactory criterion for linking particular biological systems to memory. At the conclusion of this review, we suggest a set of experimental criteria that may be helpful in identifying neurochemical systems that play a crucial role in memory.

CATECHOLAMINES

The anatomy and physiology of the catecholamine (CA) systems have been described recently in comprehensive reviews (137, 138). Behavioral pharmacological studies have suggested that CAs, notably norepinephrine (NE) and dopamine (DA), play some role in memory processes. However, the relevant literature is large and often confusing, and it still seems too early to specify exactly the nature of this role. Here we consider evidence from acute pharmacological studies with centrally active CA agonists and antagonists, studies using discrete brain lesions or 6-hydroxydopamine (6-OHDA) to deplete brains CAs, studies directed at the possible role of CAs in reward, studies of peripheral CAs, and studies involving human subjects.

Central NE and DA

A large number of studies have reported facilitation or impairment of retention following post-training, systemic administration of CA agonists or antagonists, respectively (59, 77, 139–141). Without further study, however, it cannot be assumed that systemic injections are affecting behavior

via a central action on CAs, since peripheral CAs will also be affected by these injections. Central CAs would appear to be involved, however, in the reported effects of intraventricular and localized intracerebral injections of CAs, CA agonists, and CA antagonists. Central administration of NE, DA, or the CA agonist l-isoproterenol, in amounts too small to affect behavior when given systemically, improved retention (142) and attenuated the retention deficits induced by the CA antagonists *dl*-propanolol or diethyldithiocarbamate (DDC) (143–145). Intraventricular DDC (146) or localized intracerebral injections of the CA antagonists *dl*-propanolol or *dl*-alprenolol (143, 144) impaired acquisition and retention. Despite the considerable attention that these results have been given, what they tell us about brain CAs and memory is obscured by the fact that acute manipulation of brain CAs has frequently failed to affect learning and memory (56, 147, 148). These negative findings have been reported for a range of behavioral tasks including passive and active avoidance, conditioned taste aversion, and visual discrimination. In one study, rats received one of twelve different CA antagonists immediately after one-trial passive avoidance training, and retention was tested seven days later (148). Only DDC, an inhibitor of dopamine-β-hydroxylase activity, measurably affected retention, although at least three of the other drugs decreased NE levels to an equivalent or greater degree (whole brain NE to $< 47\%$ or normal levels). It has been generally recognized that DDC exerts a variety of effects other than inhibition of NE synthesis that could account for its disruptive effects on behavior (148–150).

Taken together, the findings from studies of systemic and central administration of CA agonists and antagonists do not lead to any simple generalization about the role of central CAs in learning and memory. In subsequent studies of this type, measurement of the extent and duration of the effect on central CAs and the use of multiple behavioral tasks would seem essential if the conflicting positive and negative findings are to be sorted out.

Another way to assess the possible role of central CAs in memory has been to employ treatments capable of depleting brain CAs for relatively long periods of time. In general, such treatments do not appear to impair learning and memory in a reliable way. Thus mice treated with reserpine (4 mg/kg) 24 hr prior to passive avoidance training had normal retention despite having NE and DA reduced to about 5% of normal levels at the time of training (151). The same dose of reserpine given 2 to 5 hr prior to training did produce amnesia, although in this case NE and DA were reduced only to about 10% of normal levels at the time of training. In addition, intracisternal injections of 6-OHDA in rats sufficient to decrease whole brain NA and DA to less than 13% of normal levels did not affect acquisition or retention of a passive avoidance habit (152).

Preferential depletion of brain NE by 6-OHDA lesions of the dorsal

adrenergic bundle seems not to affect learning or memory across a wide range of appetitively and aversively motivated tasks (149, 153 and references therein). Moreover, pretraining or post-training electrolytic lesions of locus coeruleus, which can reduce NE by 60–80% in cortex and hippocampus, does not appear to affect retention (154–158).

In the case of DA, lesions of substantia nigra, which can reduce striatal DA to about 5% of normal levels (159, 160), did not disrupt passive avoidance acquisition or retention (161). Moreover, rats treated systemically with pimozide, a DA receptor blocker, learned the classical conditioning component of avoidance responding in a normal fashion (162). A role for dopaminergic pathways in memory might be inferred from the finding that post-training electrical stimulation of the substantia nigra or the caudate-putamen can disrupt passive avoidance training (159, 163). However, these results need not be taken as evidence that the nigrostriatal pathway normally participates in memory functions. This point has been made by showing that destruction of the dopaminergic, nigrostriatal pathway did not in itself disrupt retention (159). Thus, although the memory deficit produced by electrical stimulation is apparently mediated by the nigrostriatal pathway, this pathway itself does not appear to be critically involved in memory. Available evidence regarding dopaminergic-cholinergic interactions in the neostriatum (164) raises the possibility that electrical stimulation of the nigrostriatal pathway disrupts memory by causing an abnormal influence of dopamine upon cholinergic neurons. Such considerations caution against the too simple assumption that treatments affect behavior only through the particular neurotransmitter system under study.

The evidence just reviewed indicates that learning and memory can often proceed normally in the presence of combined or separate depletion of brain NE and DA. Disruption of brain CAs by lesion or drugs, however, can have dramatic and disruptive effects on active avoidance behavior (165). Attempts to deplete whole brain DA or NE preferentially by 6-OHDA (e.g. DA by 75% and NE by 24%) (152) suggest that these defects are due primarily to a reduction in brain DA. This finding and others have led to the interesting suggestion that dopaminergic pathways, particularly the nigrostriatal system, are involved specifically in motor learning and do not have a general role in memory processes (149, 162, 166, 167).

Another line of evidence linking brain CAs to memory comes from a series of studies correlating brain NE levels with retention (168, 169). A decrease in telencephalon-diencephalon NE levels to 80% of normal levels 10 min after passive avoidance training correlated with good retention in rats given one-trial passive avoidance training. Levels greater than 90% or less than 70% correlated with poor retention. These relationships appear to hold as well when various amnesic treatments are employed. For example, the α-adrenergic blocker phenoxybenzamine attenuated the amnesia

produced by pairing a high intensity, training footshock with epinephrine, and it also raised brain NE levels from about 60% to 85% of control levels at 10 min after training (169).

These studies indicate that an orderly relationship can occur between central NE and retention performance. It is not yet clear exactly what this relationships means. Brain NE levels might relate primarily to the stress associated with training or to the degree of arousal produced by the footshock. In this sense brain NE levels after passive avoidance training may vary with the specific training and treatment conditions, reflecting the familiar rule that performance is best at an optimal level of arousal. However, the finding that learning and memory can often proceed normally despite marked depletion of brain NE levels must mean at the least that the link between 80% brain NE levels and good retention is not absolute. That is, some specific level of brain NE does not appear to be required for good retention. Instead, the correlation between 80% NE levels and retention presumably speaks to some relative change in brain NE levels that ordinarily accompanies optimal training in the passive avoidance task. Moreover, this correlation might be different, or even absent, in other kinds of learning situations. In addition, since normal retention of this task can apparently occur even in animals whose brain NE has been markedly depleted (151, 152), brain NE seems not to play an essential role in the formation of memory.

Reward

Dopamine has been linked to learning and memory with the suggestion that central dopaminergic pathways might mediate the effects of reward. Evidence from electrical stimulation studies and studies of intracranial self-stimulation have suggested that the mesocortical DA system in particular may be involved in processing the rewarding consequences of behavior (170). NE does not appear to be crucial in the self-stimulation phenomenon (171–173). There is rather good correspondence between those brain sites that can sustain self-stimulation and the anatomy of dopaminergic projections. Moreover, electrical stimulation of several sites of dopamine innervation can affect retention of passive avoidance training. However, what these findings tell us about memory is complicated by the fact that the relationship between self-stimulation and natural reward is still unclear (174) and by the fact that long-term behavioral effects (i.e. memory) can develop after habituation, latent inhibition, and exploration of a novel environment—situations that do not involve conventional reward. Accordingly, information about dopamine and reward or reinforcement may apply to certain kinds of behavioral situations, but may not be relevant to many of our questions about how behavioral plasticity develops and endures.

In pursuing the relationship between DA, reward, and memory, it should

be useful to evaluate the effects of electrical stimulation of dopaminergic projection sites in tasks other than passive avoidance. In addition, investigating the effects of lesions of these pathways can help decide whether they normally play a role in memory. In the case of the nigrostriatal pathway, for example, whereas electrical stimulation impaired passive avoidance retention, lesion of the pathway did not affect retention (159). In this case then, the data do not support the idea that the dopaminergic, nigrostriatal system has a specific function in memory. The stimulation and lesion paradigm would appear to be exemplary for deciding whether a particular system normally plays a role in behavior.

Peripheral NE and DA

It now appears that some effects on memory produced by manipulations of CAs are best understood by supposing that the peripheral nervous system can have a role in the development of memory. Evidence for this view comes from a group of studies showing that the well-known facilitatory effect of post-training amphetamine on retention (77) is probably due to peripheral effects of amphetamine. First, intraperitoneal but not intraventricular injection of amphetamine facilitated retention (175). Second, *dl*-4-OH-amphetamine, a drug that primarily affects peripheral CAs, facilitated retention (176). Third, the facilitatory effects of both 4-OH amphetamine and *d*-amphetamine on memory were blocked by adrenal demedullation (176).

It also seems likely that the adrenergic antagonist reserpine effects memory by peripheral action. Syrosingopine, an analogue of reserpine that primarily depletes peripheral CAs, produced as much amnesia as reserpine (177–179). Moreover, systemic injections of NE or DA, which do not cross the blood-brain barrier in appreciable amounts, blocked the amnesia associated with syrosingopine (179). Taken together, these findings indicate that systemic injection of some drugs affects memory by their action on peripheral CAs. Given these results, the possibility must be considered that many of the catecholaminergic drugs that can affect retention may do so by affecting peripheral rather than central CAs. Peripheral CAs may normally have a modulatory action on the development of memory by mediating some of the peripheral concomitants of arousal. The importance of an experience may be related in part to the response of peripheral hormonal systems (180).

The possibility that peripheral hormones and central CAs share a role in memory functions is suggested by recent findings that combined 6-OHDA lesions of the dorsal adrenergic bundle and adrenalectomy impaired retention of active and passive avoidance, whereas these same treatments done separately were ineffective (181–184). Perhaps both peripheral hormones and brain CAs modulate memory in a cooperative way, so that ordinarily

memory can develop normally unless both these systems are disrupted. Considerable evidence does exist for mutual influences between pituitary hormones and CAs (68), but how these two systems might work together to influence memory remains unclear.

If CAs ordinarily modulate memory processes in some way, perhaps other systems are capable of compensating for NE and DA when they are absent or depleted. This possibility introduces a complicating feature to the notion of modulation as we presently understand it. Whereas the other systems that have been identified as candidates for modulators of memory processes seem to play an obligatory role (i.e. memory is impaired if the normal action of these substances is disrupted), the modulatory effect of CAs does not appear to be essential for memory to develop.

CATECHOLAMINES—HUMAN STUDIES The possibility that learning and memory in humans might be improved under some circumstances has been explored using drugs that affect CAs. It is well known that facilitatory effects of stimulants such as amphetamine and caffeine can improve performance on a variety of tasks, particularly ones that are boring or fatiguing for normal subjects. However, these drugs do not appear to be particularly effective for tasks that require concentrated intellectual effort (185). Studies of amphetamine and methylphenidate on learning and memory have involved learning-disabled children, healthy aged subjects, depressed patients, and normal adults. Facilitatory effects have been obtained most reliably in subjects presumed to be functioning suboptimally or in young children, whose information-processing capacity has not yet fully matured. Thus 20 mg *d*-amphetamine improved word recall in depressed patients (186), and a dose of 0.5 mg/kg facilitated word-list recall in normal children (187). There have been relatively few studies of stimulant drugs on memory in healthy adults. *d*-Amphetamine has been reported to facilitate (188), to impair (189), or to not affect (190) paired-associate learning. A recent study of three doses of methylphenidate (0.1, 0.25, 0.5 mg/kg, i.v.) on three memory tasks suggested that methylphenidate's primary effect was to impair performance by disrupting attention during learning (191). Methylphenidate did not exert facilitatory effects at any dose, and did not affect retention when given immediately after learning.

In evaluating the effects of these drugs on human memory, it is useful to keep in mind the findings from the large experimental animal literature in this area. The effects of catecholaminergic drugs are known to depend on task variables as well as on dose. Thus, the same post-training dose of 1.0 mg/kg *d*-amphetamine or 0.1 mg/kg epinephrine facilitated retention of avoidance training with low footshock or after extensive pretraining, but impaired retention of training after high footshock or minimal pretraining (168, 192). It has been suggested that the arousal state of the animal

interacts with a given dose of stimulant drug to determine performance (3). Facilitation of performance occurs when the level of arousal associated with training is inadequate and the drug can promote an optimal level of arousal. By this view, facilitation of retention should be difficult to obtain in healthy, optimally functioning adults. This same idea suggests why facilitatory effects of stimulant drugs may be relatively easy to demonstrate in experimental animals (77). Animals trained in the laboratory are not usually in an ethologically meaningful context, and laboratory tasks may therefore not optimize learning and memory capacity. In such situations, changes in stress or in the activity of specific transmitter systems could conceivably improve the efficiency of information processing. In healthy human subjects, however, it may be more difficult to improve on the neural machinery that has evolved for information processing.

These studies with human subjects indicate that catecholaminergic drugs can influence memory, perhaps by affecting attention, arousal, or other aspects of information encoding that occur at the time of learning. This idea is further supported by two different lines of evidence: neuropsychological studies of Korsakoff syndrome and studies of locus coeruleus function. The alcoholic Korsakoff syndrome is characterized by symmetrical lesions along the third and fourth ventricles and by a qualitatively distinct memory defect not common to all amnesias (20, 193). The amnesia appears to depend in large part on deficient encoding at the time of learning (194). The extent of this cognitive defect has been correlated to lumbar fluid levels of 3-methoxy-4-hydroxyphenyl glycol (MHPG), the primary brain metabolite of NE (195). Clonidine, an α-adrenergic agonist, improved some measures of cognitive function (196). Thus the deficient initial encoding exhibited in Korsakoff syndrome may reflect in part a deficiency in brain NE function.

Neurophysiological studies of the locus coeruleus, the major source of forebrain NE, have shown that this structure can exert modulatory influences on sensory input (197). In addition, post-training lesions of locus coeruleus do not disrupt retention (156, 158). Taken together, these considerations emphasize the possible involvement of catecholaminergic systems at the time of information input—in attention, organization of new motor programs, and other forms of information analysis—rather than in post-training, gradually developing processes required for the consolidation of enduring memory.

CONCLUSION

This review of behavioral pharmacological studies has considered six areas of investigation (acetylcholine, protein synthesis, ACTH, vasopressin, opioids, and catecholamines) in the light of our present understanding of the

neurobiology of memory. In general, the data are consistent with a view of memory whereby information storage occurs as alterations in connectivity along neural pathways already specialized for different kinds of information processing. These intrinsic, information-containing neural ensembles are not fully established at the moment of learning, but develop and change with time in a way that reflects their modulation by extrinsic systems. For example, extrinsic systems might signal the significance of previously occurring events by providing information about their consequences. Extrinsic systems can presumably influence memory in other ways as well, as indicated by the long time after learning during which the integrity of such systems can remain important (17, 20).

Table 1 summarizes current views about memory as they apply to intrinsic and extrinsic systems. Whereas this distinction seems a useful one, the assignment of particular molecules, systems or brain regions to one or the other category should be considered tentative. The difficulty of distinguishing what is modulation from what is information storage, particularly in drug studies, has been noted by others (18, 141); some have preferred to interpret the results of virtually all such studies as reflecting modulatory influences on memory storage of a nonspecific nature. We have suggested that studies with different drugs reveal distinctly different aspects of memory storage processes. Cholinergic drugs, for example, appear unique in their ability to influence memory of a particular event throughout the lifetime of the memory. Accordingly, cholinergic drugs seem best understood as effecting synaptic substrates of information storage, as originally proposed by Deutsch (21). Other substances (e.g. vasopressin, ACTH, opioid peptides), which are most effective shortly after learning, seem best understood as exerting modulatory effects on memory. Furthermore, the putative effects of these substances on arousal, fear, and attention raise the possibility that modulation reflects specific and different influences on memory, rather than some single influence.

Neuropsychological studies of amnesia have provided a particularly good example of modulation that makes just this point. Damage to the region of the dorsomedial thalamic nucleus of the diencephalon (198) or to the medial temporal lobes (15) can result in a marked defect in new learning capacity that extends across all modalities, in the absence of much loss of memory from before the onset of amnesia (20, 199). Memory is therefore not stored in these structures. Instead these structures have been considered to exert a modulatory influence at other sites on the formation and development of new memories (17, 20). Recent studies have also suggested that diencephalic and bitemporal amnesia are fundamentally different, and that these two brain regions contribute in different ways to the development of memory (200–202). Taken together, these studies confirm the usefulness of the concept of modulation and suggest in addition that modulatory influences

Table 1 Intrinsic and extrinsic memory systems[a]

Intrinsic	Reference	Extrinsic	Reference
Cholinergic neurons	22	Reticular formation ("Now print")[b]	119
Protein synthesis	14	Biogenic amines (arousal, reinforcement)	118
Morphological changes	19	ACTH, vasopressin (arousal)	3
		Peripheral catecholamines (arousal)	180
		Dopamine (reward)	170
		Opioid peptides (fear, attention)	132, 136
		Hippocampal formation (consolidation)	15, 17
		Diencephalic midline (encoding)	194

[a] Summary of views regarding intrinsic, information-containing systems and extrinsic, information-modulating systems. A wide variety of substances and structures, not mutually exclusive, have been suggested to modulate memory storage in some way. The terms in parentheses indicate the kinds of functions that have been associated with each extrinsic system.

[b] An order for all neurons recently activated to undergo growth.

need not operate by the same mechanism. One might therefore expect that the pharmacological analysis of memory should also reveal more than a single kind of modulation.

The finding that a drug can disrupt memory in a time-dependent way after training has often been taken as evidence for the existence of a modulatory process, whose characteristics are defined by the supposed pharmacological effects of the drug. Since destroying a brain region or a pathway does not always disrupt memory, even though stimulation of the region or pathway can be disruptive (159), we question whether the conventional, post-training, memory disruption experiment is in itself sufficient to postulate the existence of a memory-modulating process. At the least it will be important to distinguish between those processes that serve an obligatory function in the establishment of memory and those that do not. In addition, since events that occur close together in time are often related, it might be adaptive for the storage processes of contiguous events to influence each other. For example, the neural consequences of a second event might affect the storage of information about a just preceding event. By this view manipulation of a brain system shortly after training might disrupt memory, not because that brain system is normally important in memory, but simply because in this case storage of memory is contaminated to some extent by the storage of noise.

The following criteria may be useful in considering whether a particular brain system is critically involved in memory modulation. (*a*) a drug affecting the brain system should be time- and dose-dependent; (*b*) facilitation as well as disruption of memory should occur with appropriate manipulation of the system; (*c*) removal of the system should affect memory; (*d*)

there should be a correlation between learning and some measure of physiological or neurochemical activity of the system; (*e*) effects of manipulating the system should be obtainable across a variety of tasks, not just aversive or appetitive tasks, for example, or tasks requiring movement.

Everything known about the principle of modulation and extrinsic systems suggests that modulatory processes should operate across a variety of tasks and apply to various kinds of memory. In the case of intrinsic systems, however, we have postulated the existence of specialized and diverse networks that process and store information and that differ in part according to the kind of information that is stored, e.g. imprinting (60) or motor programs (166).

It now appears that information-processing systems can be distinctly organized to the point that some forms of memory storage do not require the usual modulatory influences. Neuropsychological study of amnesia has identified a domain of memory function that appears to be independent of the diencephalon or medial temporal regions. Amnesic patients were able to acquire a mirror-reading skill at a normal rate and to retain it at a normal level for at least three months (203). This occurred despite amnesia for having performed the task before and amnesia for the specific words that had been read. These findings have suggested a distinction between information that is based on rules or procedures and information that is based on specific-item information or data. Thus amnesic patients are able to learn and remember new rules and procedures but are unable to learn the facts or data that are ordinarily acquired by applying these rules and procedures. Moreover, procedural information is acquired normally despite damage to those brain regions known to exert an obligatory, modulatory influence on the learning of most if not all data-based information that is the topic of conventional memory research. Accordingly, modulatory processes should not be presumed to participate in all forms of learning and memory. This conclusion appears to follow in part from the diversity of organization of intrinsic systems. It seems reasonable to expect that pharmacological analysis will also illuminate differences between various modes of information processing.

Interest in the biochemical and pharmacological aspects of memory has generated an enormous amount of research relevant both to the neural basis of memory and to the goal of developing treatments for memory disorders. The facts and ideas emerging from this work seem best viewed from a neurobiological perspective that embraces the facts of cellular studies of plasticity as well as the facts of neuropsychological studies. In this way we can move toward biologically and psychologically meaningful formulations about how memory is stored, and also have the best chance to discover clinical applications of our work.

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