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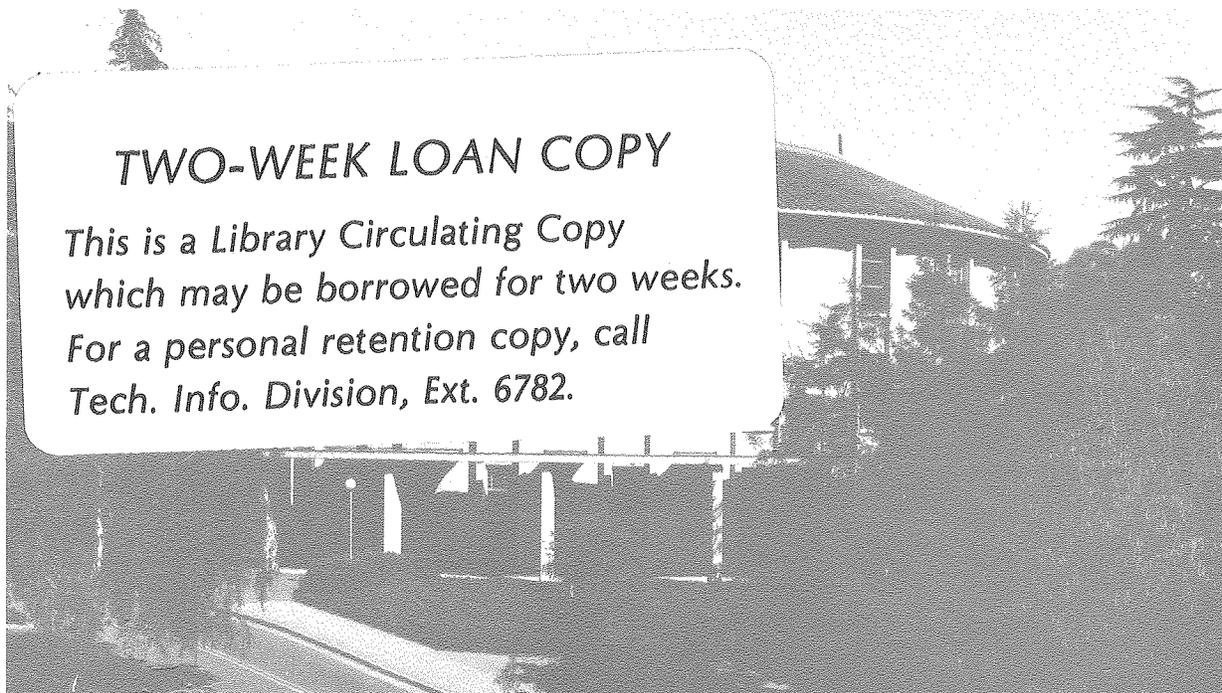
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PHARMACOLOGICAL MODULATION OF FORMATION OF LONG-TERM MEMORY*

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Evidence is now strong that a series of biochemical steps, including the synthesis of proteins is required for the synthesis of long-term memories, but other processes can modulate the formulation of memories. Schemes of memory formation involving several stages have been proposed and specific mechanisms have been hypothesized to account for these stages (e.g. Gibbs and Ng, 1977). Evidence supporting the existence of such stages has been obtained. The hypothesis that protein synthesis is required for formation of memory has stimulated much research and several recent reviews (e.g. Dunn, 1980; Rosenzweig, Bennett and Flood, 1981). But many treatments and agents that have been found to affect the formation of memory cannot be incorporated directly into this sequence of presumed basic processes. While this and other reasons have led some investigators to question or even abandon the hypothesized basic sequence, other investigators have taken up the concept that modulatory processes exist as well as basic ones. That is, the processes required for formation and expression of memory take place within a complex bodily environment where other systems or processes can influence or modulate those that participate directly in the formation of memory.

It may be worthwhile to consider explicitly the concept of modulation of memory formation for at least three reasons: (a) This may make the account of memory formation more complex and less simplistic than attending solely to the presumed direct route. It may also help to explain apparently discrepant or even opposite effects obtained with the same treatment under different conditions of training or testing. (b) It may help in explaining the selectivity of memory. (c) Applications are as likely to come from modulatory processes as from those on the direct path.

The concept of modulation of memory began to become explicit around 1970, but some of the evidence we will draw on goes back to the late 1940's when experiments showed effects of cerebral electroshock on consolidation of memory. The term modulation derives from physical models such as amplitude modulations or frequency modulations of a carrier wave, although we suspect that psychological or behavioral interactions will be more complex.

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The term has two main implications in the present context: (a) Both positive and negative effects can be produced. In fact, as we will see, a treatment that aids memory formation in some circumstances can impair it in others. (b) The primary processes are known or are becoming known, and there are other, secondary modulating influences. (This may be over-optimistic; perhaps we know only modulating and not basic processes.)

It seems likely to us that different modulating influences will be found for each of the main stages involved in learning and memory -- acquisition, storage of memory, retrieval and extinction. In fact, different modulatory influences will probably be found even for substages of these processes.

I. Examples of Modulatory Effects

A. Modulation by electrical stimulation of the nervous system

Early evidence for modulation of memory formation came from experiments concerning effects of cerebral electroshock on memory. The hypothesis that perseveration of neural activity is necessary for consolidation of memory was enunciated by Müller and Pilzecker in 1900 on the basis of experiments on human verbal learning. MacDougall promptly suggested that this hypothesis could account for the retroactive amnesia that often follows head injuries. When electroconvulsive therapy began to be used in the 1930's, reports soon appeared that this treatment could impair memory. Experiments with rats by Duncan (1949) employed posttrial cerebral electroshock treatments after each of 12 daily trials. The interference with learning was found to be greater, the closer the shock followed the trial. It was hoped that a temporal gradient could be established that would be general for different training tasks and that this would help to pinpoint the underlying biological processes. Instead, the gradient was found to vary widely with training tasks and procedures. Further research involved localized stimulation of subcortical sites, and low current intensities were found to be effective in critical locations. Moreover, facilitation was obtained under certain conditions with stimulation of the reticular formation, amygdala, or hippocampus. McGaugh et al. (1979, p. 153) have suggested the generalization that under conditions where retention would normally be good, posttrial brain stimulation often causes impairment, but under conditions where retention would be poor, brain stimulation may enhance retention.

B. Modulatory effects of pharmacological agents

1. Excitants and depressants

Pharmacological agents have long been known to affect learning and memory. McGaugh and Petrinovich (1959) showed that posttrial administration of strychnine could facilitate formation of longterm memory. They explored the temporal gradient of this effect and later extended it to other stimulants. In our own research on effects of stimulants and depressants, we have employed the technique of putting memory strength into a sensitive zone where increases or decreases can be measured readily. Setting memory strength is accomplished both by training procedures and also by the use of anisomycin (ANI), an inhibitor of protein synthesis. A few examples of results of such research are given next: When training strength and injections of ANI caused about 80% of mice to be amnesic,

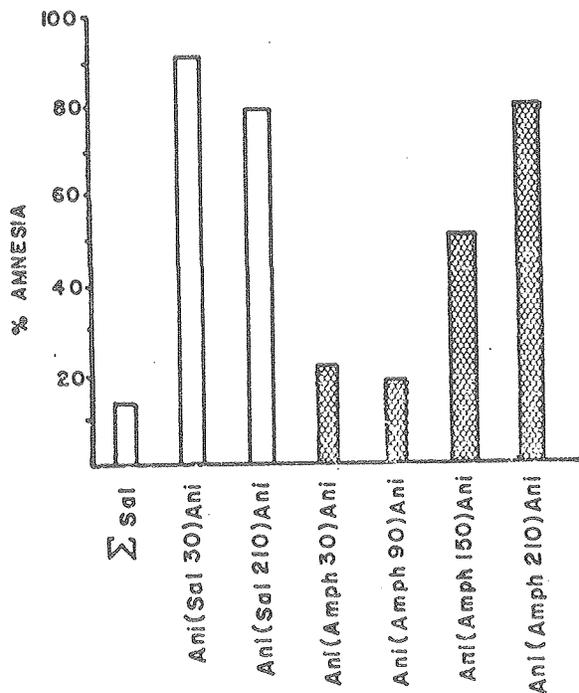


Fig. 1. Amphetamine blocked amnesia caused by anisomycin when administered 30 or 90 min. after passive avoidance training. It reduced the percentage of amnesia when given 150 min. posttraining but was ineffective at 210 min. (N = 20/group). (Figs. 1 and 2 from Bennett et al., 1979).

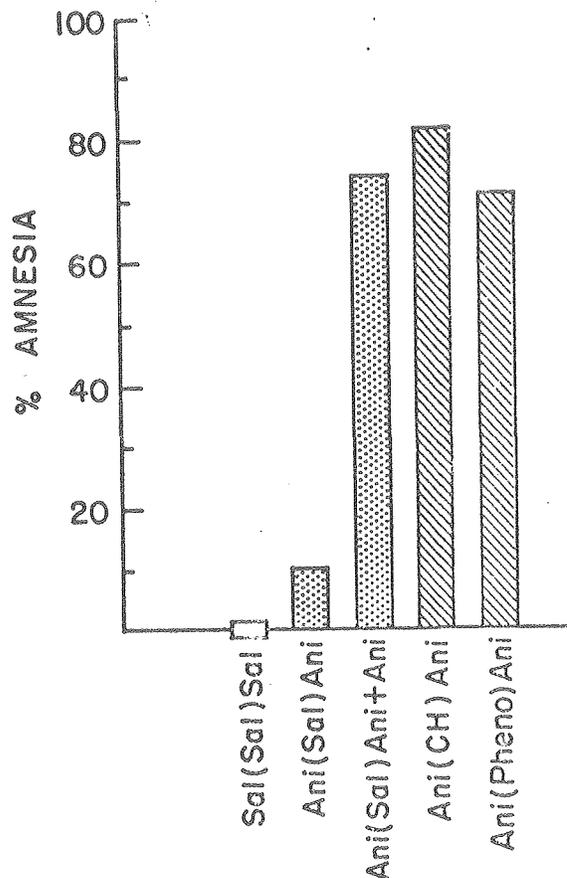


Fig. 2. Chloral hydrate (CH) or phenobarbital (Pheno) increased ANI-induced amnesia for passive avoidance training. The second of these successive injections of ANI could be replaced by one of the depressants without reducing the percentage of amnesia. (Ns of the 5 groups were 20, 20, 23, 21 and 31, respectively.)

administration of amphetamine posttrial reduced the incidence of amnesia significantly (see Figure 1). While this effect was most pronounced when the amphetamine was given 30 or 60 min. posttrial (around 20% amnesia), there was still a significant effect when amphetamine was administered 150 min. posttrial (50% amnesia); at 210 min. posttrial, amphetamine no longer affected memory. Similar positive effects of posttrial injections were found with other stimulants -- picrotoxin, strychnine, caffeine and nicotine (Flood et al., 1977, 1978). When conditions were set to yield low levels of amnesia, posttrial administration of depressants (chloral hydrate or phenobarbital) significantly increased the incidence of amnesia (Figure 2).

2. Catecholamines

Memory can also be modulated by affecting catecholamine systems. For example, administering diethylthiocarbamate (DDC) either pretrial or posttrial can impair memory if training strength is low (Bennett, Rosenzweig & Flood, 1979). This effect can be overcome by intraventricular injection of norepinephrine (NE) posttrial (Meligini et al, 1978). Thus, alterations in central NE can modulate memory formation.

But some catecholamine modulation of memory may also operate through a peripheral route, as McGaugh et al. have shown. Thus, peripheral injection of amphetamine, which causes release of NE, facilitates memory, whereas injecting amphetamine directly into the ventricles of the brain does not affect memory. Moreover, an amphetamine derivative, 4-OH-amphetamine, which does not readily enter the brain, facilitates memory in posttrial injections as much as does amphetamine, which readily enters the brain (Martinez et al., 1979). So the site where amphetamine acts to facilitate memory may not be in the brain. Amphetamines may affect memory by working on the sympathetic nervous system or other peripheral catecholaminergic systems. Support for this hypothesis comes from experiments in which removal of the adrenal medulla combined with peripheral sympathectomy was found to abolish the memory-enhancing effects of both amphetamine and 4-OH-amphetamine. These studies may help to explain how peripherally administered hormones affect formation of memory, since much evidence suggests that these hormones do not pass the blood-brain barrier. Thus, peripheral body states appear to interact with brain states to determine the efficiency of formation of memories.

3. Neuropeptides

Modulation of learning and memory by endogenous substances has been studied intensively by many investigators; see recent reviews by Bohus (1981) and De Wied (1981). It was first observed that certain hormones such as ACTH and vasopressin could affect acquisition, consolidation, and retrieval. Then it was found that fragments of hormones (such as ACTH₄₋₁₀) or even modified fragments affected learning and memory, even though these small molecules did not exert effects on the peripheral targets of the hormones. Furthermore, many of these peptides were found to be produced in the brain as well as in the pituitary, and De Wied et al. (1974) designated them as "neuropeptides." It is now considered that a large glucoprotein molecule, produced in the pituitary and in some regions of the brain, serves as the precursor for a number of behaviorally active peptides such as ACTH and related peptides, alpha- and beta-melanocyte stimulating hormone (MSH), and alpha- and beta-endorphins. The large pro-hormone has been called "pro-opiomelanocortin" or "pro-opiocortin." It has been suggested that specific enzyme systems present in the pituitary and in the brain control the formation of particular bioactive peptides from the precursor molecules (Burbach and De Wied, 1980).

The effects of posttrial injection of some neuropeptides on memory are dose-dependent, show temporal gradients, and vary in direction according to strength of training. For example, with a low level of training strength (low footshock), either of 2 doses of ACTH (3 or 6 IU) enhanced retention. With slightly stronger training, the lower dose enhanced retention but the higher dose impaired retention; with still stronger training footshock, both doses impaired retention (Gold & Van Buskirk, 1976). Thus these positive and negative modulating effects were somewhat like

those of posttrial electrical stimulation of the amygdala on retention, where interaction with training strength has also been reported.

The same neuropeptide may have effects on different stages of learning and memory. Thus ACTH and related peptides have been reported to either facilitate or inhibit consolidation of memory, depending upon dosage of posttraining injections, and also to facilitate retrieval when given just prior to the retention test. Vasopressin has also been reported to affect both consolidation and retrieval, and research with vasopressin fractions has suggested that different parts of the molecule affect the consolidation and retrieval mechanisms (Van Ree et al., 1978).

4. Neurotransmitters

The neuropeptides considered in the last section may function, at least at some sites, as synaptic transmitters. Other research has indicated that learning and memory can be modulated by operating on transmitter systems. For example, we have shown that enriched experience increases the activity of the cholinergic system in the brain (Rosenzweig et al., 1978), and Deutsch and Leibowitz (1966) have modulated this system at the time of recall. Deutsch gave rats active avoidance training and tested for recall at either 7 or 21 days. The training strength was set so that non-drug subjects recalled well at 7 days but poorly at 21 days. Some subjects were injected with DFP, an anti-cholinesterase agent, shortly before being tested for recall. DFP subjects performed significantly worse than the non-drug subjects at 7 days, but DFP subjects performed significantly better than non-drug subjects at 21 days posttraining. Deutsch's interpretation of this reversal of effects is as follows: training increased the amount of acetylcholine (ACh) released per neural impulse at certain synapses, but this declined during the weeks after training. At 7 days posttraining, DFP caused the relatively large amount of released ACh to continue its activity for a prolonged period, thus keeping post-synaptic neurons depolarized and blocking transmission; this interfered with performance of the task. At 21 days, however, the release of ACh was inadequate to produce performance (the memory trace was weak). Under these conditions, DFP aided ACh to achieve transmission. We will see later that attempts are now being made to modulate cholinergic transmission in order to improve recall of human subjects.

II. Possible Mechanisms of Modulating Effects

The preceding paragraph indicated one possible mechanism of modulation of recall, and a number of other modulatory mechanisms have been proposed. Let us consider some of these and research done to test these hypotheses, including work of our own laboratory. We will concentrate on modulation of consolidation of long-term memory.

A. Modulation of protein synthesis

Since it has been demonstrated that synthesis of protein(s) is necessary for formation of long-term memory (Bennett, Rosenzweig and Flood, 1979; Rosenzweig, Bennett and Flood, 1981), it was important to test whether other types of agents that modulate memory formation (e.g. excitant and depressant drugs) might directly alter protein synthesis. If this was true, then such modulation could be incorporated into the protein synthesis hypothesis. We have therefore tested whether the rate of protein synthesis in brain tissue is affected by several excitant and depressant

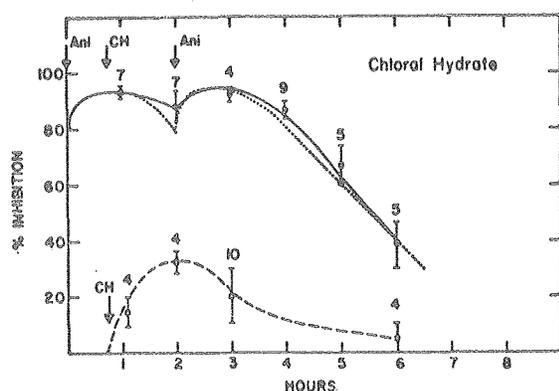


Fig. 3. Chloral hydrate (300 mg/kg) alone produces only about 30% inhibition of protein synthesis. Given in combination with ANI (.....), it does not significantly alter the inhibition caused by ANI. Results obtained with phenobarbital were similar to those for chloral hydrate. The number per group is shown at each data point. (From Flood et al., 1978.)

drugs that are effective modulators of formation of long-term memory. As an example, we found that a dose of chloral hydrate that effectively blocked formation of memory caused only a 30% reduction in rate of protein synthesis, whereas at least 80% inhibition is needed to cause amnesia. Also, whereas chloral hydrate can potentiate the amnestic action of anisomycin, chloral hydrate does not add to the level of inhibition of protein synthesis caused by anisomycin (Figure 3). Similar findings were obtained for other excitants and depressants, indicating that the effects of these agents are truly modulatory rather than playing a role in the sequence of basic processes of memory formation.

B. Affecting long-term memory through earlier stages

Some modulating agents may affect short-term or intermediate-term memory processes and through them affect formation of long-term memory. For example, excitants given prior to training or shortly after training could prolong short-term or intermediate-term processes and thus could counter the effects of inhibitors of protein synthesis; that is, they could help STM or ITM to last until the effects of inhibition wore off and then allow conversion of STM or ITM to LTM. It has, in fact, been suggested that certain treatments prolong STM because they have been found to extend the posttraining period during which electroconvulsive shock can impair formation of LTM (Quinton, 1978). We have found by direct measurement, however, that STM is not prolonged even though the lability of LTM formation is extended (H.P. Davis et al, in preparation). Even if prolongation of STM may be possible under some circumstances, this could not explain cases where formation of memory is favored when an excitant is administered only 60 min. or even 150 min. posttraining, after STM and ITM should have decayed. We showed such a positive effect of delayed administration of amphetamine above in section I.B.1.

C. Modulation by altering arousal

Modulating agents could alter levels of arousal and thus affect continued neural processing, thereby altering formation of LTM. This is consistent with observations mentioned above that memory formation can be enhanced by non-pharmacological treatments such as electrical stimulation

of brain sites. This may help to explain the selectivity of memory. Much information enters short-term storage but relatively little is stored for the long term. If some events are accompanied by motivational involvement and feedback, these may be selected for retention and the storage processes modulated accordingly. Although learning and memory may not require such feedback, they may be significantly influenced by it. We have obtained results consistent with this hypothesis (Flood et al., 1977), and further tests of this hypothesis are needed.

III. Applications to Problems of Human Cognition

If we already understood the biological mechanisms of learning, memory storage, and retrieval, this knowledge could be applied to the prevention or alleviation of many human problems. Examples of such problems include mental retardation, senility and presenile dementia, and recovery from brain injuries. Consider too the immense social consequences if the efficiency of learning and memory of normal individuals could be increased by one-tenth. Such results could present us with new problems, as we will note in the final section of this paper.

A. Examples of positive applications

There are, in fact, already indications that pharmacological agents that modulate memory formation or retrieval in laboratory animals are also effective in human beings. Let us note a few examples.

Serial verbal learning in normal human subjects has been found to be enhanced by arecholine, a cholinergic agonist, and by choline, a precursor of acetylcholine, but to be impaired by scopolamine, a cholinergic antagonist. Those subjects who were more affected by both the enhancing and impairing drugs, were the ones who showed the poor scores of the group under control conditions; in other words, these drugs may be useful in bringing individuals towards an optimal level of cholinergic activity but may not be able to improve those who are already at that level (Sitaram, Weingartner & Gillin, 1978). Both storage and retrieval of verbal material were enhanced in normal human subjects by physostigmine which inhibits the enzyme acetylcholinesterase and thus prolongs activity of acetylcholine (K.L. Davis, et al., 1978). Both Sitaram et al. and Davis et al. noted that in Alzheimer's disease and other presenile dementias the cortex shows a decrease in the enzyme that synthesizes acetylcholine, and both groups of investigators suggested that research should be done to see whether cholinergic agents might aid such patients. A subsequent pilot study with Alzheimer's disease patients has reported that while physostigmine alone did not cause improvement, there was facilitation of memory when physostigmine was coupled with lecithin, a source of choline (Peters & Levin, 1979). Perhaps these agents could also aid some kinds of retarded individuals.

Effects of neuropeptides on human memory are also being explored, and beneficial results have been reported. For example, vasopressin appears in several studies to be related to memory in human beings. Patients with diabetes insipidus, who suffer from deficiency of vasopressin, have impairments of memory (Laszlo, cited by De Wied, 1981). Treatment with vasopressin improves memory and other cognitive functions in these patients. In addition, vasopressin has been reported to reverse both amnesia that results from brain injury and amnesia that results from alcohol abuse (Oliveros et al., 1978; Le Boeuf et al., 1978). Since different parts of the vasopressin molecule may affect memory consolidation and retrieval

differentially (as noted above in section I. B. 3), and since modification of ACTH fragments has produced agents with potencies far greater than those of the original compounds, De Wied (1981) suggests "that neuropeptides will become the drugs of choice in the treatment of brain disorders."

B. Social problems that may arise from applications

Rather than terminate this review on a completely positive note, it seems prudent to sound certain reserves and warnings. For one thing, even though no unfavorable side effects seem to have been reported for the neuropeptides, investigators must be alert to such possibilities. But even if further research confirms the efficacy of these agents and their freedom from side effects, social problems related to application should be envisaged and steps taken to prepare for them. This theme was already sounded some years ago by Professor René Cassin who was awarded the Nobel Peace Prize in 1968 for a career devoted to promoting binding treaties and laws guaranteeing human rights. Late in his life, Cassin attempted to stimulate scientists, educators, and jurists to consider how biological and behavioral research bears on human rights (Rosenzweig, 1969). As Cassin pointed out, problems as well as benefits could result from the use of a new pharmacological or behavioral treatment that would significantly improve learning ability or memory. One source of difficulties is the likelihood that such beneficial treatments would, at least at the start, be applied selectively by advanced countries and, within these countries, by groups or families with greater information and financial means. This would then result in aggravating the disparities among national and social groups. Furthermore, if such advances were to be applied around the globe, would we prepare sufficiently in advance for the social consequences of a general rise in intelligence? These problems are similar to others involving technological advances, but in this case we physiologists and behavioral scientists who are participating in the research have a special responsibility for the consequences of its applications. One basic step that we can take towards promotion of consideration and eventual solution of these problems is to publicize them widely in international congresses such as the present one and in journals with international readership. Special symposia and conferences should also be addressed to these difficult social problems. Collaborative international projects of research and application can also help to promote the universality of application of research in this field. We hope that some of you who hear or read this report will want to be active not only in fostering research and application in this area but also in promoting discussion and realization of application in ways that will truly promote both the rights and the potentials of human beings around the world.

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