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BRAIN PLASTICITY, MEMORY, AND AGING, A DISCUSSION

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BRAIN PLASTICITY, MEMORY, AND AGING,
A DISCUSSION

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SUMMARY

It is generally assumed that memory faculties decline with age. A discussion of the relationship of memory and aging and the possibility of retarding the potential decline is hampered by the fact that no satisfactory explanation of memory is available in either molecular or anatomical terms. However, this lack of description of memory does not mean that there is a lack of suggested mechanisms for long-term memory storage. Present theories of memory usually include first, neurophysiological or electrical events, followed by a series of chemical events which ultimately lead to long-lasting anatomical changes in the brain. Evidence is increasing for the biochemical and anatomical plasticity of the nervous system and its importance in the normal functioning of the brain. Modification of this plasticity may be an important factor in senescence.

This discussion reports experiments which indicate that protein synthesis and anatomical changes may be involved in long-term memory storage. Environmental influences can produce quantitative differences in brain anatomy and in behavior. In experimental animals, enriched environments lead to more complex anatomical patterns than do colony or impoverished environments. This raises fundamental questions about the adequacy of the isolated animal which is frequently being used as a model for aging research. A more important applied question is the role of social and intellectual stimulation in influencing aging of the human brain.
With this audience, it is not necessary to emphasize the importance of neural function and the importance of preserving that function for as long as possible. Unfortunately, as Dr. Cherkin mentioned earlier, we know little about the mechanism(s) of formation of long-term memory, and this makes the problem of understanding the effects of age on neural function a difficult one. Since Dr. Cherkin did not review as much as I had anticipated concerning the mechanisms of memory formation, I will outline a model here. (From conversations with Dr. Cherkin, I can say that he and I are in substantial agreement on many aspects of a model for the formation of long-term memory.) The observations of Professor Cotman's group on brain plasticity may have intriguing implications for memory, and I will mention some related findings of our group at Berkeley which has focused on brain plasticity for a number of years.

Model of Memory Formation

To guide research in this area, it is helpful to have a model, and we like to use the model published by Dr. Shashoua (Fig. 1) [14]. In this model he suggests that sensory stimuli perceived by the organism are subsequently transduced through short-term electrical and chemical events and some of this information is eventually entered into a long-term form of storage in the neuronal membrane.

Our focus is on the mechanisms involved in the long-term storage. It is now generally accepted that a number of chemical steps are involved; many investigators have concentrated on the formation of new RNA as a key step involved in long-term memory storage [10,12]. Our research has led us to emphasize the importance of the formation of protein and, perhaps, its transport down the axon to the synapse with subsequent modification of the membrane, or even the formation of new synapses. That is, the last steps depicted in Fig. 1 are key factors. We tend to place less emphasis on the speculations that suggest that the production of new and unique
molecules is the critical element in the formation of long-term memory. Our biases, and we admit that these are biases, would hold that in forming memories we are making more of the same kinds of neuronal molecules that we would be normally synthesizing.

Anisomycin, A Protein Synthesis Inhibitor, and Memory

At this point, I would like to describe briefly a method we have used quite successfully to study the involvement of protein synthesis in the formation of long-term memory. In addition, we have developed a paradigm to study the effects of other drugs that may modify the formation of memory.

The drug that we have used is anisomycin (ANI) (Fig. 2), an inhibitor of protein synthesis. I am sure that you are aware of studies of memory formation using puromycin or cyloheximide. We believe that ANI is a superior drug for such studies, at least in the mouse. ANI effectively inhibits protein synthesis by preventing transpeptidation. In the mouse, a dose of ANI that is far from lethal produces inhibition of protein synthesis for several hours, whereas near lethal doses of cycloheximide are required to produce equivalent inhibition of protein synthesis. As a result of the low toxicity of ANI, one can control the time course and duration of inhibition of cerebral protein synthesis by administering successive doses of ANI at 2 h intervals (Fig. 3).

During the past several years we have investigated the effectiveness of ANI as an amnestic agent in a variety of passive and active-avoidance behavioral tasks schematically depicted in Fig. 4. Using the passive avoidance step-through test as an example for the present discussion, we found some years ago that as one increases the number of doses of ANI one obtained increasing amnesia, but the particular shape of the curve relating amnesia and inhibition of protein synthesis depended greatly on factors to
which Dr. Cherkin alluded to in his introduction—training strength (which
is influenced by many parameters, including the behavioral test employed
intensity and duration of footshock), duration of the interval between
the training and testing, and strain of the mouse. If the training is
marginal and the test is difficult, then one dose of ANI may produce amnesia.
With stronger training, several successive doses may be required to cause
amnesia. By varying these factors, one can get a dose-response curve of
the relationship of long-term memory formation to training strength and
to the duration of inhibition of protein synthesis. Furthermore, it has
been found that inhibition of protein synthesis by ANI will cause amnesia
for a variety of training tasks, including tasks learned for positive as
well as for negative reinforcement [7]..

Drug Influences on Memory Formation

Let me now turn to another aspect of our studies with ANI. In these
studies, ANI has been used in combination with post-trial injections of
a number of pharmacological agents in order to evaluate the effects of
the latter drugs on memory formation and, in the process, to learn more
concerning the mechanisms of memory formation. Typically, in such investiga-
tions, the drug has been given prior to the training task, and one has
the problem of trying to dissociate the drug's effects on training and
on memory formation. We have developed a paradigm that allows us to circumvent
this difficulty. Normally, ANI is given 15 min prior to training, and
then one or more additional doses are given at 2 h intervals. At some
time after the training, one can give a dose of the drug of interest, perhaps
an excitant, such as methamphetamine or strychine, a depressant such as
chloral hydrate or phenobarbital, ACTH derivatives, etc. [6,8,9]. The
effect of depressants on ANI-induced amnesia are shown in Fig. 5. Under the
training and testing conditions used in this experiment, two doses of ANI did
not produce amnesia, but three successive doses did. If a depressant such
as chloral hydrate or phenobarbital was administered after training instead of a dose of ANI, the mice also became amnesic. The opposite effect can be seen if one uses a stimulant. In this case, a sufficient number of doses of ANI are administered to produce amnesia, and then a stimulant such as strychnine, picrotoxin, or methamphetamine is given post-training. These stimulants counteract the ANI-induced amnesia.

At this time, it might be useful to think of some sort of construct as to how these effects may be explained. Experiments showed that the effects of the stimulant and depressant drugs on memory could not be explained in terms of direct effects on protein synthesis; neither type of drug had sufficient effect on synthesis to alter memory. Rather, we interpret their effects on memory in terms of level of arousal following acquisition; this plays an important role in determining the length of time over which the biosynthetic phase of memory will last [8]. Fig. 6 [4] shows simplified curves not too different from that presented by Dr. Cherkin [3]. Units on the axes, "days after training" and "strengths of memory," are arbitrary. The several curves represent the strengths of memory formation under several conditions. If the training strength is marginal, the memory strength may not even reach a level where we would say that memory formation had occurred. We suggest that while long-term memory formation is taking place, factors such as a stimulant can in some manner increase the rate of long-term memory formation.

We believe this paradigm in which ANI-treated mice are given post-trial injections of the drug of interest will be useful to screen the potential of drugs to facilitate or accelerate the formation of long-term memory. It would be of interest to use this system to test some of the drugs that Dr. Scott will be discussing later in this symposium.
In a recent experiment we have shown that colchicine given shortly after training is also an effective amnesic agent. Colchicine blocks transport of materials down the neural axons but does not affect neural impulses. We interpret the results as a demonstration that the protein which is synthesized in the cell body must be transported down to the synaptic endings: we do not yet know how it is deposited there, but ultimately it produces a change in synaptic function, and therefore a long-lasting effect which we refer to as "memory" [2].

Effects of Environment on Brain Function

At this point, let me take up briefly another aspect of our research which may be of particular importance for aging--that is, study of effects of differential environments.

We have heard several speakers at this symposium refer to environment as a hostile sort of influence. On the contrary, we believe that the environment and external stimuli may be necessary for the normal function of the animal. Frankly, we are concerned about some experiments now being reported with older animals because we fear that the environments employed may have limited the value of the results. The pathogen-free animals that investigators are using frequently in aging studies probably have had reduced environmental stimulation throughout their lives. That is, they have been raised in what we would characterize as an "Impoverished Condition". Experiments that we have carried out over many years, and that we will describe briefly here, demonstrate that there are measurable effects in the brain depending upon the environment in which the animal has been raised. We would also like to suggest that the environment may be useful as therapy to promote the recovery of the animal from brain injury.
Three main environmental conditions have been used to provide differential experience to animals, typically from 30 to 60 days of age. We refer to these conditions as Enriched, Standard Colony, or Impoverished, but it should be clear that "enriched" and "impoverished" are used only in a relative sense. In the Enriched Condition (EC) a dozen rats are maintained in a cage about 75 cm square containing rat "toys," that is numerous objects with which the rat can interact. These objects are changed daily. A more typical sort of environment for the laboratory rat is the Standard Colony (SC), in which 3 rats live in a cage 20 x 32 cm with no added inanimate objects. The third environment is the "Impoverished Condition" (IC), and this may be the one which most closely approximates that of the pathogen-free animal. In IC a single animal lives in a cage the same size as that used for SC. Among the differences we have found between animals raised in EC and IC, and to a lesser extent between EC and SC animals, are increased weight and thickness of cerebral cortex, and increased ratio of RNA to DNA. (The RNA/DNA ratio may be our best single measure for distinguishing between EC and IC raised rats). Dr. W.T. Greenough at the University of Illinois and Dr. Marian C. Diamond in our group have found changes in parameters such as synaptic density, synaptic length, and dendritic branching. In other words, we have evidence that an enriched environment when compared to an impoverished environment leads to measurable morphological and biochemical changes in the brain of rats [1,11].

We have not done a great deal of work with older animals, but some years ago Dr. Walter Riege in our laboratory compared the responsiveness of rats when they were placed into enriched or impoverished environments at ages as late as approximately 300 days. He found that animals at all ages were
responsive to enriched environment with an increase in the ratio of cortex weight to subcortex weight (Fig. 7) [13]. We would like to have data out to 700 days of age or so in order to provide a more definite answer for truly aged rats. Extrapolating from these results, we would like to suggest that we should be concerned with the environments and stimulation that animals (including human beings) receive throughout their lifetime, and we will return to this point shortly.

Meanwhile, let us note that environmental factors may be particularly important during recovery from brain lesions. To test this, we have asked what kind of effects from differential environments would one find in animals with lesions made in occipital cortex. In recent experiments, we compared the behavioral test scores in a Hebb-Williams maze test of both brain-lesioned and non-lesioned rats raised postoperatively in EC, SC, and IC. We have confirmed previous observations that intact rats raised in EC do better than SC or IC raised rats in the maze test. We have also found that the lesioned animals maintained in EC made fewer errors than the lesioned rats maintained in SC or IC; this is true whether the lesions were made neonatally [16], or shortly after weaning [17] or in young adult rats [15]. Questions were addressed here to Dr. Cotman (and we raised this point to him a few years ago) as to whether recovery measured in anatomical terms can be hastened by appropriate stimulation and he is now investigating that aspect.

The facts that an enriched environment helps to overcome the behavioral effects of surgical brain lesions and that even fully adult animals respond to environmental enrichment raise the question whether enriched experience would also help to maintain intellectual function during aging [5]. The loss of cells that occurs in advanced age as well as the probability of at least small cerebrovascular accidents indicates that the aging brain is likely to
be suffering from naturally occurring lesions. In this case, ongoing enriched experience might provide concurrent therapy. Dr. Cherkin has already suggested that individuals who keep active intellectually may show less decline of the nervous system, although it may be difficult to separate cause and effect here.

In summary, we believe that experiments that are being carried out in many laboratories with young and young-adult animals do raise questions and suggest directions for experiments being carried out with animal models of much greater ages. While there is still much to find about neural mechanisms of learning and memory, we do not believe it is necessary to wait to begin to carry out related experiments with the aged.

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FIGURE LEGENDS

Figure 1. A model for long-term memory storage proposed by Shashoua [14]. In this model for information storage, sensory input from the environment is perceived by sensory receptors (eyes, ears, nose, skin, etc.) and transduced through several electrical transformations into short-term chemical changes. These are subsequently elaborated into long lasting membrane changes. Reprinted from [14].

Figure 2. Anisomycin (ANI), 2-p-methoxyphenylmethyl-3-acetoxy-4-hydroxypyrrolididine (C_{14}H_{19}NO_{4}) is an effective inhibitor of cerebral protein synthesis and also a powerful amnestic agent in mice.

Figure 3. The inhibition of cerebral protein synthesis obtained in Swiss-Webster male mice from one (---o---), two (---o---), and three (---o---) successive subcutaneous injections of 0.5 mg of ANI. The number of animals used and the standard deviation of each data point are shown. Taken from [6].

Figure 4. Schematic representation of four types of behavioral apparatuses useful for studying memory. The step-down task is normally used as a passive-avoidance task; the step-through test can be used as a passive or active avoidance task. In the passive avoidance task, the animal must remain either on the platform or in the small compartment to avoid shock; in the active avoidance test, the animal must move to the larger compartment on the right, frequently after a cue such as a bell or light, to avoid shock. For the
pole-jump, the animal must jump onto the pole to avoid shock. The T-maze may be used as either a spatial (right-left) or a visual (light-dark) discrimination task. The relative difficulty of these tasks is approximately in the order named, but can vary with the exact details of the training procedure.

Figure 5. The effect of chloral hydrate (CH) and phenobarbital (Pheno) on ANI-induced amnesia. The depressants were administered ip 30 min after training in the step-through passive avoidance task. ANI was administered 15 min prior to training, and 1 3/4 h or 1 3/4 and 3 3/4 h after training. The amnesia produced by 2 doses of ANI and the depressant was significantly greater than that produced by only 2 doses of ANI and approximately equal to that produced by 3 doses of ANI. Taken from [6].

Figure 6. Schematic representations of the strength of memory traces as a function of time after training. Memory for a given training test will depend upon a number of factors including number of trails, length and intensity of shock, etc. Events occurring after training can either increase or decrease the nature of the "strength of memory trace" curve and will determine if the behavioral criterion used to measure the memory will be reached and thus if the subject is "amnesic" or "non-amnesic". Taken from [4].
Figure 7. Cortical/Subcortical weight ratio of rats raised in standard colony conditions and then placed in enriched or impoverished environment for 30 or more days at 25, 60, 105, and 285 days of age. At each age, the ratio of cortex/subcortex weight was higher for rats placed in EC, and lower for rats placed in IC than for the rats maintained in standard colony conditions.

Enriched (EC), (X — — — — X); Impoverished (IC), (0 — — — 0);
or Standard Colony (SC), (— — — — ).
A THEORETICAL MODEL FOR INFORMATION STORAGE
(Shashoua, 1972)

ENVIRONMENT

SENSORY INPUT
(Light, Heat, Chemical, or Mechanical)

SENSORY RECEPTORS

TRANSDUCTIONS

ELECTRICAL-TIME

DIGITAL

ELECTRICAL-SPACE

ANALOG

TEMPORARY CHEMICAL-SPACE

SYNAPSE

LONG TERM CHEMICAL

RNA

PROTEINS

POLYSOME

MEMBRANES

XBL758-4205 A
Fig. 3
Bennett-Rosenzweig
EFFECT OF DEPRESSANTS ON ANI-INDUCED AMNESIA

% AMNESIA

Sal(Sal) Sal  Ani(Sal) Ani-Ani  Ani(CH) Ani  Ani(Pheno) Ani

XBL763-5725
MEMORY STRENGTH

DAYS AFTER TRAINING

STRENGTH OF MEMORY TRACE

Behavioral Criterion

XBL 775-4390

Fig. 6
Bennett-Rosenzweig
Figure 7
Bennett and Rosenzweig
DISCUSSION OF MEMORY AND AGING SESSION

Q. (Dr. Cherkin) If you recall that initial simplified notion of how memory works on my slide, I showed that when we train our animals (chicks) just moderately with an attenuated aversion and test them a day later they have forgotten the task, but if the subjects are trained in that weakened manner and then administered a stimulant drug and tested the next day, they remember. The subjects behave just as though they had been strongly trained. This I suggested, is a model for sensory disfunction, as explaining some of the memory disfunction of the elderly. What you have just shown us is that the training strength can be kept constant, and later, one can manipulate memory information at the consolidation phase by inhibiting brain protein synthesis, administering stimulant after that, and restoring memory. This is very encouraging, I think, for our efforts to enhance memory in the elderly by pharmacologic methods. It means that memory function is not an all or none business; memory is multifunctional, and an impairment at one step might be compensated by an improvement in another step, and this would be wonderful.

A. (Bennett) There may actually be a trick in our experiments, and we are thinking of several possible interpretations. It may be that when protein synthesis is inhibited, that the phase of memory which Dr. Cherkin has referred to a short-term memory is somehow prolonged. The stimulants are actually strengthening that phase rather than operating on long-term memory formation itself. However, the strength of the short-term memory may determine the efficacy of conversion to long-term memory. One reason that we need to know much more about the conversion of long-term memory is that frequently supplements such as RNA hydrolysates are advocated for the elderly, and I believe it is quite questionable whether any of these have any real value. The use of RNA supplements arose from the period when
there was a great deal more speculation than now concerning the role of RNA and protein synthesis in memory formation. People were even considering molecules, either RNA or protein, in which memory could be encoded and even transferred from one subject to another. I think there is much less speculation of this nature at the present time.

Q. (Gerson) The Old Testament says that kidneys participate in some of the mental functions with the brain--I don't know if you can take it at face value or not. However, when one works with drugs like puromycin, cycloheximide, or colchicine, which are injected into an animal my question is: Is the end result which is measured due to the effect on the brain, or the kidneys, or the liver, of other things? Do you have any means of determining what is the primary action of the drug?

A. (Bennett) I think using a combination of drugs and a combination of behavioral paradigms indeed one does. With respect to ANI, for example, one of the rather fortunate aspects of its action is that it inhibits protein synthesis in the brain much more and much longer than it does in peripheral organs such as the liver. In the mouse, there is very little inhibition in the liver whereas brain protein synthesis is inhibited a great deal [3]. I think another way to get at this is by studying the time parameters of protein synthesis inhibition in brain and the resulting amnesia. For example, we have an experiment in which we delay the administration of ANI under conditions which I will term "strong training". We do not obtain amnesia if protein synthesis is allowed to proceed for as little as 2 min after the training, but do get amnesia if little or no protein synthesis occurs immediately after training. It is this experiment, which I have not discussed in detail here, that provides the evidence which we believe rules out the necessity of derepression of DNA and the production of new messenger RNA, and then the production of protein as the normal route to
establish long-term memory [1]. So my construct says that actually what is happening is a site-specific or cell-specific acceleration of protein in selected neuronal pathways using preexisting RNA. Now there is a great deal of discussion between Quartermain, Flexner, and us about the various roles of the catecholamines. Quartermain has reported that protein synthesis inhibitor-induced amnesia can be reversed by adrenergic receptor stimulation [4,5]. We find, and Squire at San Diego finds, that one can have larger changes in dopamine than produced by ANI without producing amnesia. We find that drugs acting on the catecholamine systems are much less effective than ANI in modifying memory processes. That is not to say that they do not participate importantly in the establishment of long-term memory. We cannot and do not rule out the role of dopamine, norepinephrine, serotonin, etc.

Q. (Cherkin) Getting back to Dr. Gerson's question haven't there been experiments in which cerebral injections have produced amnesia, but peripheral injections do not?

A. (Bennett) Oh, certainly. Dunn recently noted that emetine and pactamycin did not enter the brain well, but did inhibit peripheral protein synthesis. They were not effective amnesic agents [2]. Dr. Flood is now studying the site specificity and efficacy as an amnesic agent of very small quantities of ANI injected locally into selected brain regions. There is a very nice story developing of interactions between ANI and other drugs on a site selective basis.

Q. (Strehler) With the occipital lesions, was there any impairment in vision?

A. (Bennett) We did not measure vision in this test. Actually, even blinded rats can solve Hebb-Williams mazes quite well. The primary focus
of that particular experiment was not whether the lesion produced a deficit on problem-solving, but the effect of environment. Even if there had been an effect on vision, it would not have affected our interpretation of the results.

Q. (Strehler) The other question I had concerned the considerable degree of homology in the fingerprints of both the tubulin digests and the neuronal filament digests. How many amino acid substitutions would be necessary to produce the non-matching spots?

A. (Selkoe) I don't think that really is known. The homology between tubulin and neuronal filament protein is minimal, less than 10% of the peptides. We are talking here about long peptides. My impression is that there is not a great deal of homology of peptides between tubulin and neuronal filament protein. There is much more homology between glia fibrils and neural filaments. But I don't think we really know to what extent amino acid substitution would lead to a greater or lesser degree of overlap.

Q. (Strehler) What about Alzheimer's and

A. (Selkoe) The peptides have not been carefully mapped. I did not have time to mention one study that has been done, showing that there was a 51,000 MW band that is enriched in similar fractions of and Alzheimer's. However, it seems like it is a glial contaminant and that is why I spent some time discussing the role of glial protein. It looks like those samples taken from areas of highly gliotic cortex, as in the case of the hippocampus, and we don't think that the isolated protein is the neural filament. All we have so far is immunofluorescent studies which I indicated
but not an isolation yet. We plan to use our techniques soon to do just that.

Q. (Nathan) Is there any karyotypic difference in Alzheimer's and Down's syndrome?

A. (Selkoe) The karyotype is basically normal in Alzheimer's disease. There was a study published in Science approximately a year ago showing that the incidence of Down's syndrome was heightened in first-order relatives of individuals with Alzheimer's disease. The figures were rather small, something like 2% of a large series of first-order relatives of Alzheimer's patients had Down's. There is no direct evidence of a chromosomal correlate of Alzheimer's disease, just this very weak evidence in terms of a possible Down's history.

Q. (Strehler) Have any studies been done with

A. (Selkoe) No, they have not been done.

Q. (?) Are there any possible relationships between maternal age and Alzheimer's disease?

A. (Selkoe) I have never heard that question asked. It is an interesting question. I have no data on that at all. At the various symposia that I have attended on this subject, I have not heard anyone say yea or nay.

Q. (Meites) Can you expand on the function of the postulated new protein that you believe is involved in learning and memory?

A. (Bennett) If we assume that the new protein is involved in long-term memory storage, and obviously some of us would like to make that assumption, its function remains the critical problem. Here is a very simplified sort of construct that we would propose (and many others can be made at this time): protein is formed in the cell body, it moves on down to the synaptic junction and somehow modifies that junction in a rather permanent way.
One may raise the question, then, how does that junction stay modified when you have continued turnover of the cell constituents? It is quite accepted that there are no proteins in the brain which last the lifetime of the animal. One analogy that might be used here would be something like a chimney. If you have a chimney constructed, and then a brick falls out of the chimney (the brick representing the molecule, the chimney the modified synaptic ending), then the brick can be replaced rather easily, it doesn't take much imagination to see how a new brick can be put into its proper place in the chimney. This is a rather crude analogy, but there is increasing evidence of increased synaptic density and synaptic function, that is increased anatomical complexity, with what we term "enriched environments". In other experiments which I didn't discuss today, we have used a paradigm which we believe will be accepted as a learning paradigm without the accompanying social interaction. Using this paradigm we have shown changes in the RNA/DNA ratio of the cortex and increases in cortical weight in those animals that must solve mazes to get their food and water. We would now like to demonstrate synaptic changes in these problem-solving animals. The results I am discussing are primarily in the cerebral cortex. People have looked for differences in other brain areas, and there may be some changes in the hippocampus, but subcortical differences are generally small or not detectable as yet.

Q. ( ? ) What about changes outside of the brain?

A. (Bennett) I guess people haven't really looked there. Most of us would expect the primary changes would occur in the brain.

( ? ) In those experiments where stimulants have been given after the training task, and improved performance was obtained, have you used some of the common stimulants?

A. (Bennett) Yes. We have used nicotine, caffeine, strychnine, and methamphetamine. I think what is common about these drugs is that they
are all classified as stimulants, rather than that one acts on the adrenergic system, another on the cholinergic, etc. It should be noted that Dr. James McGaugh at one time hoped that memory could be understood largely in terms of one neurotransmitter. As more research results have become available, it appears that there is a critical balance, and a number of drugs can modify memory processes.
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