1974); (4) decrease in oxidative phosphorylation by the same cells; (5) activity only when added to the blood side of the toad bladder and peritubular surface of the isolated nephrone segment.

We have found natriuretic factor to be present in greatly increased quantities in both blood and urine in uraemia; hence its rate of production must be increased in uraemia. Moreover, the natriuretic response per nephron to a fixed amount of natriuretic is markedly increased in uraemia, thus indicating that the sensitivity to the factor is increased in uraemia (Fine et al., 1976a,b).

Recent attempts to purify natriuretic factor are as follows. (1) The active fraction from Sephadex G-25 chromatography was further fractionated by using high-pressure liquid chromatography with cation-exchange H70 (Hamilton). Six fractions were obtained (Fig. 1a). Only the first, F(1), inhibited the short-circuit current (22.2±4.1%; six experiments). The others has no significant effect on the short-circuit current. (2) By re-chromatography of fraction F(1) in the same system under different conditions of elution, six separate fractions (A–F) were identified (Fig. 1b). Only two of these (A and B) inhibited the short-circuit current (15.1±2.1 and 11.2±2.2%; 11 experiments). Both were fluorescent, but only fraction B contained fluorescamine-sensitive primary amines.

These data on the isolation of natriuretic factor with high-pressure liquid chromatography system seem promising. The use of fluorescamine in the detector system makes the procedure very sensitive (Bohlen et al., 1975). By using discontinuous-stream sampling of the column effluent, sample consumption is minimized. Typically, 5–10% of the column eluate is used for monitoring, and the remainder can be used for bioassay or other analytical purposes (Radhakrishnan et al., 1977).

To date the most highly purified biologically active peptide-containing fraction, has the following characteristics: it contains no free amino acids before hydrolysis, but neutral and acidic amino acids (mainly glycine) after hydrolysis; it is non-volatile, lipid-insoluble, temperature-resistant and inactivated by pH 10.5.

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NEURONAL AND SYNAPTIC ADAPTATION
Colloquium organized on behalf of the Neurochemical Group by A. I. Matus (London)

Cellular Basis for Long-Term Neuronal Adaptation
J. Z. YOUNG
Wellcome Institute for the History of Medicine, 183 Euston Road, London NW1 2BP, U.K.

Nervous systems that are able to adapt or to learn are initially provided, by heredity, with redundant networks that allow alternative possible routes. In mammals feature
detectors in the cortex are largely laid down before birth; this has been established for
cells of the visual systems of cats, monkeys and sheep (Blakemore & Cooper, 1970; 
Hubel & Wiesel, 1977; Ramachandran et al., 1977). In human babies of 1 month, 
detectors especially sensitive to human speech sounds are already present (Eimas et al., 
1971). Detectors for complex features are not necessarily single cells, but may be 
quite elaborate modules of many cells. Each unit must have two or more possible output 
connections, allowing for alternative actions. The process of learning consists of 
limiting the pathways to those that provide behaviour appropriate to the environment 
that is encountered.

The existence of a large excess of possible pathways, even in the adult, has been 
established by Wall and his colleagues (Basbaum & Wall, 1976). They have found that 
neurons deprived of their original connections quickly come to respond to unusual 
inputs. This is often a rapid change produced by removal of previous inhibition, but may 
later include growth of new connections, such as have been shown to be formed in the 
septum (Raisman & Field, 1973).

Normal development and learning therefore consists of making selections among sets 
of modules. Mechanisms for doing this are known to mature at especially sensitive 
periods of development. In kittens or monkeys lack of suitable visual experience, even 
for a few hours, causes atrophy of the deprived cortical feature detectors. In humans 
there are critical periods for the formation of attachment, somewhat similar to those for 
imprinting in birds or mammals. There are also critical periods for learning language 
and many other capacities (Young, 1978).

These developmental processes obviously depend on the presence of special programs 
for the appearance of neurons, with appropriate biochemical properties making them 
sensitive to critical inputs. All memory formation involves neurons programmed to allow 
rapid change in their connections. Learning takes place very quickly and growth processes 
are surely too slow to be the main agent, at least in the early stages of memory formation. 
It must depend on altering the probabilities of conduction in existing pathways. This 
can be either by facilitation of those that are used or by closure of unwanted ones. The 
latter is probably the initial event in the formation of a memory record. It is likely 
to be the result of actions by small local circuit neurons (microneurons), such as are 
known to be the agents of short-term inhibition of reciprocal spinal reflexes.

The first stage of memory formation is likely to be a change in the pattern of protein 
synthesis in cells programmed to make such changes on receipt of specific signals. 
This may have the effect of producing additional enzymes synthesizing inhibitory 
transmitter or increased inhibitory receptors closing the unwanted pathways, allowing 
use of the appropriate circuits on subsequent occasions. No doubt these also later 
become increasingly powerful while the unwanted connections atrophy and disappear. 
This hypothesis accounts for the changes that are known to occur in nucleotide 
metabolism and protein synthesis during memory consolidation.

Further localization of the site and nature of these changes depends on identification 
of the modules among which selection is made during learning. In the mnemonic system 
suggested for octopus they have been considered as simple feature detectors with alter-
native outputs (Young, 1965). In mammals they are likely to be much more complicated 
sets of cells. Groups of some 10000 cortical cells have been suggested as such unit 
modules independently by Dr. G. Edelman (personal communication) and Dr. J. C. 
Eccles (Popper & Eccles, 1977). Unfortunately there is little evidence to support the 
choice of this or any other number of cells, and we have no knowledge of the switching 
systems that might be involved in restricting their outputs.

Progress in the study of the biochemistry of memory will depend on the discovery of 
methods for the identification of these units and of the changes that take place in their 
connections. A useful hypothesis is that the local-circuit neurons, with larger groups of 
cells, are specifically triggered to respond to appropriate sets of signals. This they 
do by changing their pattern of synthesis of enzymes by which they produce transmitter. 
The mechanism must be such as to provide rapid change in the probability of con-
duction among several pre-existing pathways.

1978
The Possible Significance for Learning of Some Different Types of Synaptic Modification

A. R. GARDNER-MEDWIN

Department of Physiology, University College London, London WC1E 6BT, U.K.

This short review deals with some of the types of synaptic modification which might underlie memory. It concentrates on points arising from theoretical work which are likely to be of particular interest to experimental scientists. At present it is not possible to assess whether synaptic modifications caused by particular patterns of activity are the basis of memory. Nevertheless the hypothesis has proved a stimulating one for both theoretical and experimental work.

The word synapse is used here to indicate the mechanism, possibly involving many synaptic boutons, by which one neuron influences the generation of action potentials in another. If this influence is found to be altered in a particular experimental situation, we can ask a number of questions about the phenomenon. For example:

1. What precisely has changed?
2. What circumstances are necessary and sufficient to cause the change?
3. Do similar changes occur in association with learning?

I wish to focus attention on Question 2, because it provides a major point of contact at the present time between theory and experiment. This should not detract from the importance of Questions 1 and 3, which are discussed by Kandel (1976) for many of the situations about which most is known.

In discussing whether a particular type of synaptic modification might provide a building block for a learning mechanism, it is important to consider the conditions under which a synapse is modified, and to what extent these are independent of the conditions for modifying other synapses. The actual change may occur in different ways with much the same effect on the overall synaptic influence. Thus an increase in transmitter release may have almost the same effect as (i) a reduced local uptake and destruction of transmitter, or (ii) an increase in local postsynaptic sensitivity, or (iii) a change in the geometry of a dendritic spine. On the other hand, an increase in transmitter release requiring frequent activation of synaptic terminals may sometimes, but not always, occur in the same circumstances as one which is caused by raised extracellular K+ concentration, or one requiring both frequent activation of terminals and also a powerful activation of adjacent dendritic membrane.

The discussion of possible building blocks for learning was considerably stimulated by the work of Brindley (1967; see also Brindley, 1974). Though this was by no means the first discussion, it showed that careful arguments can be used to infer something about the characteristics of modifiable elements underlying learned behaviour, even without knowing the configurations of the networks in which they are incorporated. The conclusion of most interest for neurophysiologists was that synapses which alter their strength under conditions that depend only on the firing of the presynaptic neuron are not, with the kinds of assumptions commonly made for modelling the behaviour of neural networks, capable of forming the basis of more than the most elementary learning tasks. It looked as if post-tetanic potentiation (PTP: a phenomenon in which action potentials sent down a motor axon at a high rate result in an increase in

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