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

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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

transmitter release for a variable and sometimes lengthy period afterwards) was no longer a strong candidate for the mechanism of learning, since it can occur in the presence of the drug curare, i.e. with the postsynaptic response largely blocked and only the presynaptic axons made active (Liley & North, 1953).

This conclusion is correct for certain assumptions about the nervous system. If, however, neurons work in such a way that impulses at low rates can have significant excitatory or inhibitory effects but higher frequencies are required to bring about modifications, then purely presynaptic modifications can provide the basis for complex learning behaviour (Figs. 1 and 2 of Gardner-Medwin, 1969). This does not contradict Brindley (1967), but it reinstates post-tetanic potentiation once again as a possible candidate for the basis of learning in realistic networks.

Networks using simple synapses, with only presynaptic conditions for modification, are often more complex than those that can be devised with other types of postulated modifiable synapse (Gardner-Medwin, 1969). Models using synapses which are strengthened by a simultaneous association of pre- and post-synaptic firing (Hebb, 1949) can solve many learning tasks with elegance and with little wasted capacity (see e.g. Longuet-Higgins *et al.*, 1970). Here we have the basis for two kinds of argument which can lead one to prefer some of the more complex postulated modification conditions. The first stems from the fact that the configurations of cells that arise with the use of such synapses may bear a strong resemblance (both qualitative and quantitative) to configurations of real neurons (e.g. Marr, 1969, 1970, 1971; Gardner-Medwin, 1976). The second is that the usable memory capacity in a network will normally be much greater if the modification conditions permit the synapses to be modified independently of each other (Brindley, 1969; Gardner-Medwin, 1969). Thus with post-tetanic potentiation, or with the homosynaptic depression responsible for some forms of habituation in *Aplysia* (Kandel, 1976), or with heterosynaptic facilitation (Burke, 1967; Kandel, 1976), the number of independent modifications which can be made is limited to the total number of cells. Mechanisms which place simultaneous conditions on the activity in two or more cells (e.g. Hebb, 1949; Marr, 1969; Stent, 1973; see below) permit the number of independent modifications to be equal to the number of synapses between separate pairs of cells, which in the mammalian cerebral cortex exceeds the number of cells by a factor of 10^2 and possibly much more (Cragg, 1967).

Suggestions for types of modification conditions that would permit independent changes at separate synapses have arisen from both experimental and theoretical work. Work on the dentate area of the hippocampal formation suggests that some synaptic terminals may become potentiated when both they and other nearby terminals or cells are strongly activated (Bliss & Gardner-Medwin, 1973; McNaughton *et al.*, 1978). Thus the potentiation appears to be homosynaptic (in the sense that it is restricted to those terminals that are activated), yet it is more pronounced if other terminals are simultaneously activated. It remains to be shown whether the underlying mechanism might permit fully independent potentiation of separate synapses; however, the phenomenon is interesting, and could be indicative of the kinds of mechanism proposed in theoretical work.

Hebb (1949) suggested that a strengthening of the excitatory influence of one cell (A) upon another (B) might occur when cell A contributed to the successful firing of cell B. In some theoretical work an extreme version of this postulate is preferred, in which cell A is supposed initially to have no excitatory influence upon B, until after paired activity has occurred in the two cells [e.g. in the synapses on to output cells performing recognition and classification tasks (Marr, 1969, 1970) and in the collateral synapses between output cells subserving recall (Marr, 1971; Gardner-Medwin, 1976)]. In these situations the existence of an initial excitatory influence before modification would be detrimental, though it might be conjectured that an initial inhibitory influence before modification could be beneficial, since it could provide negative weight for features in the test situation which did not match the training situation.

Marr (1970, 1971) makes a distinction between these extreme synapses, which he calls Hebb synapses, and the less extreme synapses which have a weak excitatory effect even

before they are modified, referred to as Brindley synapses. Strictly speaking, a Brindley synapse is the same thing as was originally postulated by Hebb. The nomenclature is justified, however, by the fact that Brindley (1969) first employed synapses with the Hebb modification conditions in a situation where an unmodifiable excitatory component is of positive value. This benefit is more fully developed in Marr's work (1970, 1971), where Brindley synapses aid in the selection of suitable features of events to use as the basis of the coding in the nervous system for recall and classification. Marr (1970, section 4.2) argues that it is not always possible to use genetically laid down principles or prior experience to determine a satisfactory way of coding new inputs. When such principles are lacking, the best procedure is to select some subsets of all the elements which might contribute to events, and to code events in terms of those subsets (or *codons*) in which more than a certain fraction of the elements are active. This procedure manages, roughly speaking, to make the coded versions for certain groups of similar events overlap as much as possible, while minimizing the overlap between the coded versions of dissimilar events. If the selected subsets are chosen to be ones which match better than average with some chosen event (as can easily be arranged using Brindley synapses), then the group of events which are coded in a similar way will consist of those which are themselves similar to the chosen event.

Marr (1970) discusses two additional ways in which his ideas for codon formation might be implemented, both of them rather less satisfactory than Brindley synapses but nevertheless plausible. The first uses synapses which are excitatory, but which weaken if they are inactive at times when their postsynaptic neuron is strongly activated. This is a type of modifiable synapse favoured by Stent (1973), as a plausible means of explaining aspects of the plasticity of the mammalian visual cortex. Though it is undoubtedly a possible candidate for the basis of learning, it is made unattractive in Marr's model by the fact that most of the afferent synapses on to one cell will normally be modified together, and that consequently the learning capacity of such a set of synapses will be used up very extravagantly. In Marr's theories, as in many, it is usually assumed that at any one time only a small proportion of the cells are strongly active, in the sense that they exceed the threshold activity levels involved in modification conditions. The opposite assumption (that most of the cells are active most of the time) would render Stent's 1973 modification conditions more attractive than Hebb's; but it has yet to be demonstrated whether a theory with these assumptions could be viable. Such considerations are important for experimental work, for in essence they determine whether in order to achieve experimental modifications it is likely to be necessary to activate cells or to silence them.

Marr also considers a special anatomical arrangement similar to the climbing fibres in the cerebellum as a means of determining modification conditions. A synapse from a cell A on to a cell B is, according to this postulate, strengthened if activity in A occurs at the same time as activity in a third cell whose axon (the climbing fibre) extends all over the dendrites of cell B. This could work either through some direct influence of the climbing fibre on the terminals of cell A or, if the climbing fibre causes a powerful excitation of B, through a Hebb modification condition. This arrangement is well suited for a device whose task is to recognize the combinations of activity in its afferent input at specified times and to respond in future when these occur again. Marr (1969) proposed that this task might be the function of the Purkinje cells in the cerebellum, a theory which has not been supported by experimental work, but which remains disconcertingly attractive. Climbing fibres are also appropriate in Marr's (1970) neocortex model, as the basis for modification at the inputs on to classification cells, though they are less satisfactory than Brindley synapses for the development of subset codes. The advantage seen for the special characteristic of climbing fibres (their exhaustive ramifications over the dendrites of their target cells) is that it ensures that the postsynaptic component of the modification is satisfied in an all-or-none fashion for all the terminals on a cell. Without climbing fibres this might perhaps be possible if, as has been suggested, dendritic action potentials in some cells may propagate throughout the branches of the dendrites after the soma has fired (Jefferys, 1975).

It is part of Marr's (1970) theory for neocortex that certain cells in the brain ('classification units') have the ability to pick out clusters of events with substantial similarities from amongst the events which have been experienced, and to fire in such a way as to give a measure of the similarity of a new event to one of these clusters. In order for new classification units to develop, that is for suitable cells to be chosen or altered in accordance with recent experiences, it is necessary for modifications to take place while the nervous system is working in a special mode with sensory inputs excluded. Thus the synapses might be modifiable only at certain times, and it is proposed that sleep might provide the appropriate conditions (Marr, 1970). This important idea leads to the suggestion that the modification process (perhaps involving Hebb or other local modification conditions) might also require special chemical conditions in the general environment of brain cells, or the influence of some widespread neural system. Here again we have a point worth the consideration of experimental workers who may be frustrated at the difficulties of establishing conditions under which synaptic modification can be demonstrated.

The chief aim here has been to present the case for considering relatively complex hypothetical synapses as possible candidates for the basis of memory. Some of the more complex proposals (e.g. Griffith, 1966; Uttley, 1975; Von der Marlsburg, 1973; Carol, 1977) have been omitted not because they lack plausibility or usefulness, but because it is hoped that many of the points of interest to an experimental worker may have been more clearly illustrated with simpler examples. It should be borne in mind that even the very simple types of modifiable synapse *might* be the basis of memory and may have advantages which are not at present evident. Furthermore, several different types of modification may of course be involved. The question of the duration of possible synaptic changes in relation to short- and long-term memory is an important one and is discussed elsewhere (Gardner-Medwin, 1969; Kandel, 1976).

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Macromolecular Mechanisms and Long-Term Changes in Behaviour

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There are three ways in which the adult nervous system must be able to respond to information impinging upon it from the external environment. First, it must be able to signal faithfully and in as invariant a way as possible the nature of the information and, depending on its analysis, the appropriate response. This is the function of a relatively