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Some Facts and Hypotheses Concerning Dendritic Spines and Learning

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I want to begin with two statements:

1. I will limit myself to dendritic spines (10) in the cerebral cortex. Spines in different parts of the nervous system may have different functions.
2. By learning I mean the fixation of information from the environment in the fine structure of the brain. This, most likely, is achieved by a process which sets up or changes the connections between the nerve cells as a consequence of sensory stimulation.

In the course of the last 10 years several papers have appeared indicating that the growth of spines on pyramidal cells can be influenced by the environment. Surgical intervention (enucleation of one eye, severing the optic radiation, or section of the corpus callosum) in young animals resulted in a lower than normal number of spines on apical dendrites in the visual cortex (4,13). Even the simple procedure of rearing animals in the dark had an effect. The changes appeared in the number of spines (12), in the shape of the spines (5), or in the rate of the increase of the number of spines (14). "Enriched environments" gave results which went in the opposite direction to those of deprivation (3,8). The higher number of spines in the auditory cortex following visual or somatic deafferentiation (7) could perhaps be interpreted as a compensatory effect. These findings were especially interesting, since it had been shown (6) that spines are the sites of most synaptic connections on the dendritic tree of pyramidal cells. This led to the idea that spines could be the result of learning processes.

I shall first summarize a piece of work (11) that operated under this assumption and then reflect on some recent evidence in order to show that the idea of spines as memory traces is still very obscure.

VARIATIONS IN THE NUMBER OF SPINES ON PYRAMIDAL CELLS

In Golgi preparations of the mouse, pyramidal cells can occasionally be found with much fewer spines than their neighbours.

Various interpretations are possible:

1. The pyramidal cells, poor in spines, are not so healthy, perhaps atrophic or not well stained.

2. Under the assumption that spines are memory traces, perhaps some cells have learned more than others.

3. Possibly pyramidal cells do not mature synchronously, the cells with few spines perhaps being the immature ones.

There was no support of the first interpretation, that of pathology (11). In connection with a functional interpretation of the number of spines as a result of learning processes, it was interesting to establish that the spine density is a property of the entire neuron and not only of parts of it. The densities of spines on the apical and on the basal dendrites of the same neuron are correlated.

We may draw the conclusion that if spines are memory traces, the condition for the establishment of such an engram is not only a local condition but is also dictated by the entire neuron.

But are they really memory traces?

POSSIBLE ROLES OF SPINES IN LEARNING

Figure 1 shows some pyramidal cells of a newborn mouse. They have an apical dendrite but hardly any basal dendrites yet and practically no spines. The mouse at that time is quite helpless in its behaviour. So, the development of spines might coincide with the period of learning.

However, a look at the pyramidal cells of a newborn guinea pig (Fig. 2) casts some doubt on this. They have well-developed apical and basal dendrites, densely covered with spines, resembling the dendrites of a 13-day-old mouse. The behaviour of the newborn guinea pig is also more advanced than that of the newborn mouse. It can see, it walks around, and soon begins to eat solid food.

If we do not want to assume that guinea pigs do most of their learning in the womb, the presence of spines on their dendrites at birth suggests that spines are not the result of but the condition for learning. The 13-day-old mouse and the newborn guinea pig have in common that they are at an age when they begin to explore the environment. We may suppose that the appearance of spines inaugurates the critical period of learning. In fact, if we look at the mouse at the 13th day of life, when it just begins to open its eyes, we notice that it already has half of its spines in the visual cortex (14).

A spine, then, could represent, so to speak, the right to acquire a synapse, and only the decision as to which of the neighbouring axonal elements will become presynaptic to the spine could be made later on the basis of experience.

The following observation is compatible with this idea. Figure 3 shows two spines from the first layer of the mouse cortex. On serial sections we could convince ourselves that most of the spines (all the spines we analysed)

FIG. 1. Golgi-stained pyramidal cells of a 1-day-old mouse. ×164.

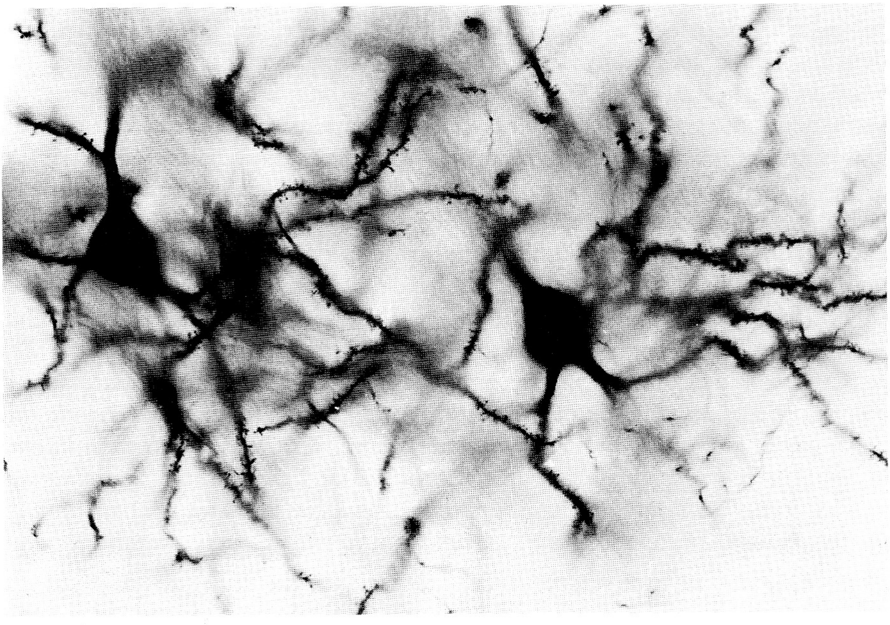

FIG. 2. Basal dendrites of Golgi-stained pyramidal cells of a newborn guinea pig. ×525.

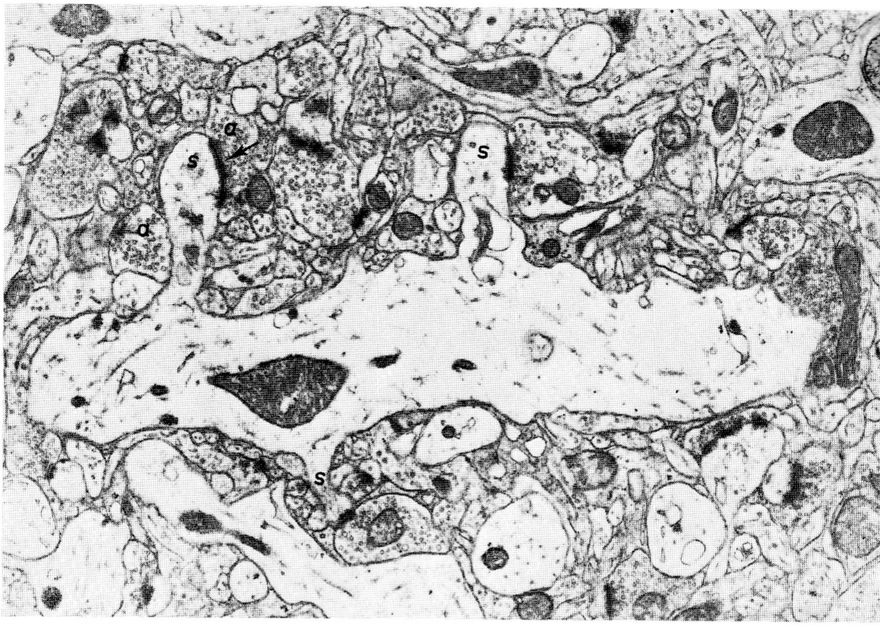

FIG. 3. Electron microscopic section of a series showing a piece of dendrite with three spines **(s)**. The spine to the left is touched by two axons **(a)** full of vesicles, but makes only one synapse **(arrow).** ×15,670.

have only one presynaptic terminal (see, however, ref. 2). It was also evident, however, that many if not all the spines are touched by more than one axon (e.g., the left spine in Fig. 3). Of the 10 spines which I followed on serial sections, six had their heads directly contiguous with one or two large axons full of vesicles with which they did not form synapses, besides the one which was presynaptic to them. In the other four cases, the additional neighbours were smaller segments of axons without vesicles or elements which could not be identified. This observation supports the assumption that the establishment of a synapse on a spine is a true choice of one out of several presynaptic candidates.

This idea leads to a new interpretation of the role of dendritic spines. The growth of spines provides a larger choice of presynaptic candidates available for the establishment of synapses. Actually, the number of axons touching a pyramidal cell may increase more than proportionally to the increase of the surface (which increases by about 70%[1]). Fibers that pass by the dendrite stay in contact with its surface for a longer stretch than they do on the spines, because of the stronger curvature of the spine head. This

[1] With 18 spines per 10 μm of dendritic length, a surface of 1.75 μm^2 on each spine and a dendritic diameter of 1.34 μm.

means that a given area on the surface of a spine can be touched by more elements than the same area on the surface of a dendrite. In the favorable case of a spine that can direct its tip toward a chosen axon, the number of reachable neighbours would be still higher than in the case of a rigid spine.

Nevertheless, we are not sure if the spines of the guinea pig at birth or those of the mouse at the beginning of its learning period are without synaptic contacts. In fact, the idea of the spine representing the right to acquire a synapse would imply that during the early learning period there should be many spines without synapses in the tissue. Nobody, to my knowledge, has given such a demonstration for the cortex. The increase in the number of synapses follows a curve which parallels that of the increase in the number of spines (Fig. 4). It is not possible yet to tell from the available data (1,9,14,15) whether or not the appearance of synapses lags behind that of spines.

In this connection I want to mention an interesting observation. In the rat, 10^9 synapses/mm^3 (1) or 6×10^{11} synapses in the whole cortex are established in 26 days. If the rat is awake half of the time, this means that 5×10^5 synapses must be established every second in the whole cortex. If the establishment of a synapse is a memory trace, it is difficult to imagine where this large amount of information comes from in the early days in the life of a rat.

DISCUSSION

If we consider the fact that spines can be influenced by the environment but that many of them appear before stimuli from the environment can have access to the brain, and if we do not want to assume that spines before birth are formed by a different mechanism than those after birth, there are two possibilities:

(1) Spines are formed at a certain time during the process of maturation. Synaptic contacts are made later as a result of sensory stimulation, or, if they are already present before, they might be provisional and wait for modification by neuronal activity. In any case, spines can be interpreted as the condition for learning. The results of deprivation experiments could be explained by supposing that spines with useless contacts disappear again, or that the further maturation of the cell and the increase in the number of spines is hindered or delayed by the deprivation (see also ref. 14).

(2) The formation of spines is not simply a consequence of the maturation of the cell but depends on neuronal activity. The formation of spines due to sensory stimulation—spines as memory traces—would be a special case, preceded by the formation of spines due to neuronal excitation induced by internal activity (the so-called spontaneous activity). For us it makes a great difference, because connections that can be influenced by the environment we call "learned," and connections that are established before stimuli from

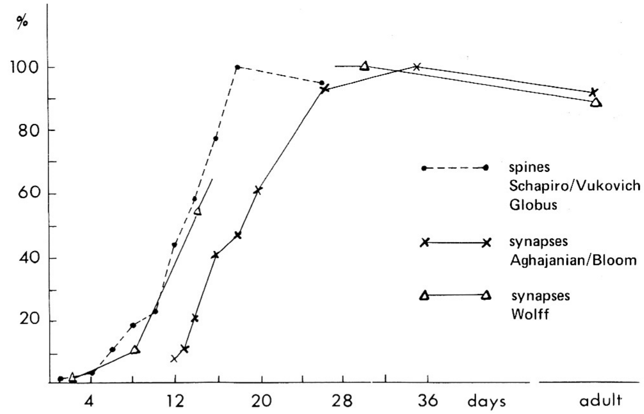

FIG. 4. Comparison between the increase with age in the number of spines and that of synapses in the cortex of the rat. The curve of spines **(broken lines)** shows the average number of spines on apical and basal dendrites in the visual cortex. The values of Wolff are taken from the uppermost tenth of the visual cortex, those of Aghajanian and Bloom from the first layer of the parietal cortex. The number of spines and synapses is expressed in percent of the maximal value.

outside can have access to the brain we call "inborn." It may be the same for the mechanism that makes spines and synapses.

We cannot yet decide between possibility (1) or (2).

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