

REVIEWS

Neurospecific Proteins and Memory

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The review reports on the experimental models that are used in studies of memory formation (in particular, passive avoidance training) and on brain structures, which have special relevance to this phenomenon. The advanced knowledge about the sequence of neurochemical processes that occur in the synaptic mechanisms during fixation of a memory trace is analyzed. The special role of neurospecific proteins (in particular, the cell adhesion proteins) in plastic modifications of the neuronal links relevant to memory is emphasized. Attention is drawn to the general features of the mechanisms providing the development of nerve tissue and memory formation.

Keywords: neurospecific proteins, memory, passive avoidance training, hyperstriatum, *lobus parolfactorius*, NCAM, cadherin.

INTRODUCTION

Memory and learning have always interested people. For a long time, people used learning in their everyday purposes and observed the respective process in animals. It is beyond doubt that memory and learning are related with the central nervous system, but for a long time nothing was known about concrete physiological mechanisms of these processes.

In 1950, the psychologist Lashley stated that memory traces (engrams) do not specifically relate to one structure or another but are diffusely distributed within the entire brain [1]. The ideas of Lashley dominated in science for a long time, and years and years of experimental work were needed to refute those conclusions. A modern approach to the investigation of the mechanisms of memory was laid by Hebb. According to the interpretation of his ideas by present-day authors [2], the phenomena of memory and thinking are provided by the activity of definite neuronal ensembles. After excitation of a neuron, which is the component of such an ensemble, its synaptic connections become more efficient. This can be associated with a short-time increase

in the transsynaptic excitability (in this case, short-term memory) or with stable synaptic alterations, i.e., with synaptic plasticity in the strict sense of this term (a possible basis for long-term memory). The results of joint studies of morphologists, biochemists, and neurophysiologists allow one to consider these ideas as the most adequate.

To inquire into the changes that occur in synapses during learning, it was necessary to develop the relevant experimental models. The necessary peculiarities for such a model should be as follows: a maximum standard pattern and minimum influences of the factors that are not of significant importance for realization of a basic phenomenon. A considerable part of modern investigations in this direction are focused on associative learning, which, to a great extent, presents a simplification of the occurring events. Undoubtedly, the human memory and different forms of acquired behavior in animals cannot be entirely reduced to associative models. Now, the models connected with aversive learning, when positive reinforcement (food) is avoided by animals, enjoy wide popularity with domestic and foreign scholars. In scientific literature, these models are called passive avoidance conditioned reflexes (PACR) or passive avoidance training (PAT).

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MODELS OF PAT

The first model of PAT was developed on chicks in 1969 [3], and since then it has been used with slight modifications in a number of laboratories. The advanced model of PAT on birds [4-6] is based on such an experiment. One-day-old chicks (*Gallus domesticus*) were placed into specialized pens, where they were taught to peck at a small (2.5 mm in diameter) white bead (genetically determined behavior), and then they were offered a larger bead coated with a bitter tasting substance, methylantranilate. After pecking the bitter bead, chicks manifested a stereotypical behavior characteristic of the aversion reaction.

It should be noted that methylantranilate is one of the strongest aversants. Some time after training (from 30 min to 24 h), chicks were offered an identical bead containing no aversant substance. The birds which refused to peck the bead were considered to have learned. Such birds exceeded 80% of the total number of those taken for the experiment. A control group contained birds which were offered a water-coated bead during training. The above-described experimental model was used to test amnesic or nootropic effects of various drugs. In this case the substances which can presumably exert an amnesic or nootropic effect were injected into the chick brain prior to or after learning.

The PAT model has also been developed on rats [7]. The experimental device in this case consisted of two sections, a large illuminated and a small dark chamber connected with a round opening; the floor of the small chamber was electrified. For PAT, an adult rat was placed in the middle of the illuminated chamber with its tail directed to the opening into the dark chamber. Investigating the illuminated space, the animal found the opening into the dark chamber and entered it (like pecking at a presumably edible object in chicks, the avoidance of illuminated space in rats is a manifestation of genetically determined behavior). The latent period of the reaction was measured as the time elapsed between placing the rat in the device and its complete transition into the dark chamber. An alternating current (50 Hz, 2-3 sec), whose intensity was enough to ensure a nociceptive effect of electrocutaneous stimulation, was fed into the lattice dark chamber floor 15 sec later. The opening between chambers was left open. The rat escaped from the dark chamber to the illuminated one and was observed for 3 min. If the animal did not come back during this time, PAT was considered to be successful from the very first attempt. Rats that returned to the dark chamber during the test interval (3 min) were excluded from the experiment.

The next important stage in the investigation of the learning process was the study of brain structures specifically involved in this process.

LOCALIZATION OF LEARNING-RELATED CHANGES IN THE NERVOUS SYSTEM

The first findings concerning localization of changes related to the formation of a memory trace were obtained by Horn [8], who studied the imprinting phenomenon in chicks. If within a short period soon after hatching a chick sees a visually well-structured object, it becomes attached to it and will learn to follow the object. It turned out that in this case in the chick brain the incorporation of labeled uracil into RNA of the medial part of the *hyperstriatum ventrale* (*IMHV*) is selectively enhanced. Other laboratories reported that during imprinting the uptake of 2-deoxyglucose changes in the same brain region [2]. With the PAT model in chicks, a considerable accumulation of 2-deoxyglucose [9] was observed in two brain regions 30 min after the avoidance training. These are the above-mentioned *IMHV* region and the *lobus parolfactorius* (*LPO*).

According to many authors [10], the *IMHV* in birds fulfils functions analogous to those of the mammalian hippocampus, and in the avian brain, the *LPO* can be an analog of the basal ganglia in mammals, but this region also receives information from the olfactory region. There is no direct (monosynaptic) connections between the *LPO* and *IMHV*; however, contact is established through the archistriatum [11].

It should be noted that the right- and left-hemisphere *IMHV* differ in the intensity of radioactive label uptake. The most intense uptake of 2-deoxyglucose was observed in the *IMHV* of the left brain hemisphere, as compared with its right part [6]. Attempts to obtain explanations for this phenomenon were undertaken in the experiments [4], the results of which are schematically illustrated in Fig. 1. If the chick left and right *IMHV* (Fig. 1A, a) or only the left *IMHV* (A, c) was damaged before training using the PAT approach, this resulted in amnesia of the acquired behavior. Lesion of only the right *IMHV* did not produce such an effect (A, b), i.e., the acquired habit remained. Thus, it can be thought that just the left hemisphere plays the role of peculiar "input" for the corresponding information.

If the *IMHV* of both hemispheres were damaged after the training procedure was completed, the amnesic effect was not observed (Fig. 1A, d). The authors [4] suggest that in this case information on the acquired habit can be transferred not only from the left *IMHV* to