The Action of Mexidol on the State of Conditioned Reflex Activity after Traumatic Brain Lesions

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It is demonstrated that even partial damage to the hippocampus is accompanied by impairments to counting time intervals lasting several months (1200–1500 presentations) without alteration of other complex conditioned reflex responses. After treatment with mexidol, which has a wide spectrum of actions, particularly antioxidant, antihypoxic, and antistress, rats showed a normal process of acquisition of a conditioned reflex to time. Unlike animals of the control group, there was no prolonged period during which there was complete impairment of the mechanism for counting time intervals. Thanks to significant improvements in autonomic processes and emotional-motivational responses, experiments could use a large number of conditioned stimuli. For example, after brain trauma mexidol strengthened compensatory-restorative processes: animals showed accelerated recovery of impaired functions, with decreases in the rate of retrograde degeneration of brain areas directly connected to the damaged parts, phenomena such as Monakow diaschisis were not observed, and so on.

One of the most important questions in any cerebral pathology is the possibility of increasing the brain’s reserve capacities. A variety of methods are used for this purpose: 1) prolonged training (mental and physical), which allows non-functioning nerve cells and conducting pathways to be “triggered;” 2) pharmacological correction of changes, particularly with antioxidants, which have recently found ever wider use. Our long-term complex studies have addressed the effects of mexidol on the process of aging and a variety of stress states [14]. These experiments demonstrated that mexidol can also be used for the prophylaxis of structural-functional changes and for increasing the reserve capacities of the brain at the integral, organ, cellular, and subcellular levels.

Recent years have seen significant increases in the incidence of cranio-cerebral trauma. Contemporary medicine has few effective substances for treating these conditions, particularly in the acute and rehabilitation periods. Mexidol, which was synthesized by Smirnov and Dyumaev [19], has a wide spectrum of actions, particularly antioxidant and antihypoxic. It inhibits the processes of lipid peroxidation, induces a complex of membrane-stabilizing effects, alters the permeability and phospholipid composition of biomembranes, etc. At the same time, data have been obtained showed that important components of the pathogenesis of brain trauma include activation of lipid peroxidation, disruption of neuron biomembranes, derangement in the systems regulating free-radical processes leading to significant levels of free radical release, as well as acute impairment of cerebral circulation, hypoxia, etc. [1, 2, 5–9, 15–18, 20].

The aim of the present work was to seek possible enhancements in compensatory-restorative processes in the body after traumatic brain lesions. Aims were: 1) to study the effects of hippocampal damage on the acquisition, dynamics, and state of conditioned reflex activity over long periods of time; 2) to study the effects of mexidol on the state of higher nervous activity after hippocampal lesions.

METHODS

Experiments were performed using Wistar rats using a food-related motor method. Conditioned reflexes (CR)
were developed in all animals to actual and trace stimuli: CR to time (counting of time intervals) and temporospatial differentiation, where, apart from orientation in space, the rats also had to count the duration of the conditioned signal. As shown by our previous data, CR to time and temporospatial differentiation are associated with different brain structures [11, 12].

Rats were placed in a chamber, which contained a reinforcement platform. On presentation of the conditioned stimulus, rats climbed onto the platform and received food from an aperture in the chamber wall. A single actual stimulus (a tone) was used, with a strict temporal stereotype: the duration of the conditioned signal was 5–10 sec in different animals, and the interval between stimuli was 60 sec; each experiment included 10–15 combinations. After fixation of the CR to the actual stimulus (the tone), sequential omission of one, two, three, and more signals was started. Rats gradually started to operate in the “pure” time regime, i.e., without use of actual stimuli in the experiment – they acquired a CR to time. This CR was regarded as correct when there was no more than one intersignal excursion over a period of 60 sec; the error tolerance for responses to time was ±10 sec.

During acquisition of temporospatial differentiation, rats were placed in the start sector of a T- or Y-shaped maze. On presentation of a tone for 10 sec (T₁₀), animals received food in the right-hand sector, while presentation of a tone lasting 3 sec (T₃) was associated with food in the left-hand sector. Signals were presented in random order. Processing of experimental data included determination of the numbers of correct and incorrect responses (separately for each stimulus and combined for both stimuli), along with null reactions (refusals to decide), and responses with instant correction of errors.

Experiments were conducted over 12–15 months; experimental animals were divided into three groups. Rats of group 1 were used for investigations of the acquisition and state of the CR over prolonged periods of time without surgical intervention (n = 30), animals of group 2 were used for assessment of conditioned reflex activity after lesioning of the hippocampus (n = 13). The state of the CR in group 3 rats was evaluated after lesioning of the hippocampus on a background of mexidol treatment (n = 11). Rats of this group received daily doses of water-soluble mexidol (100 mg/kg) during drinking, presented as three one-month courses with 30-day intervals between courses. Animals of the two latter groups were trained to the CR to the tone, used as a strict temporal stereotype, before surgery.

Hippocampal lesions were produced by I. V. Viktorov using an excitatory amino acid, i.e., quinolinic acid, injected into the hippocampus with a Hamilton microsyringe [13]. The authors would like to express their thanks for this assistance.

Lesions were assessed morphologically by embedding rat brains in paraffin. Frontal sections were stained by the Nissl method.

The dynamics of the state of the CR to time was analyzed statistically in the first two groups of rats using the t test for independent signs.

RESULTS

In intact rats, the CR to the tone developed over 10–30 combinations; the number of correct response reached 90–100% and in most animals remained at this level throughout the study period. The CR to the tone was regarded as fixed when the proportion of correct responses was at least 80% during 20 presentations.

Mathematical analysis of the results obtained from studies of the acquisition of the CR to the tone and the CR to time was based not only on the proportion of correct responses, but also the relative accuracy of counting the time interval \( m_N \), which is a measure of the displacement of intersignal responses to the end of the interval. The parameter was calculated as [3]

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m_N = \frac{\sum_{i=1}^{n_N} \Delta t_i}{t}, \quad (i = 1,2,3, ..., n),
\]

where \( n_N \) is the total number of responses during the intersignal period of duration \( t \) after the \( N \)th combination, \( \Delta t_i \) is the size of the interval between the start of the stimulus and the appearance of intersignal reactions at the end of this time interval.

At the beginning of CR acquisition, there were many intersignal reactions distributed throughout the whole of the interstimulus interval; \( m_N \) was 0.40–0.60. By tone presentation 40–50 and sometimes by presentation 60–80, intersig-