PHYSIOLOGY

Dopamine-Dependent Pathology and Trace Processes

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So-called analogs of evoked potentials can be regarded as a reliable criterion for assessing the transformation of trace processes in outpacing excitation. Dogs were injected with the dopamine antagonist haloperidol at the stage of stabilization of a motor conditioned reflex. The configuration of the evoked potential analogs in the motor cortex and basal ganglia became of the same type, without visible pathological symptoms. Evoked potential analogs with simple and complex (M) configuration were recorded after administration of L-DOPA. Specific distortions of trace processes were observed at subclinical stages of dopamine pathology.

Key Words: *analogues of evoked potentials; dopamine-related disorder; trace processes*

It has been generally accepted that prediction is based on the memorizing of biologically significant situations. Experiments have shown that probabilistic prediction is based on the formation of trace processes which gradually transform into outpacing excitation [2,4]. So-called analogs of evoked potentials (EP) or the dynamics of the reproduction of EP configuration during the intersignal period are an objective criterion for the assessment of trace processes [1,4].

Stabilization of EP parameters and configuration during training suggests that the ratio of afferentations to a given brain structure is not random and reflects the functional role of this structure. The emergence of EP analogs indicates that the reproduction of the traces of the given afferentation complex is necessary for the solution of adaptive task. In fact, typical EP analogs exist for each structure at each level of training [4,5].

During training the dynamics of EP analogs first lags behind than outpaces the EP dynamics. Consequently, EP analogs react earlier than EP to changes in afferentations. This is particularly important for situations when the afferentation complexes are pathologically distorted; this occurs, for example, in modeled DOPA-dependent symptoms. The restriction of motor afferent complexes was observed in neuroleptical parkinsonism; psychomotor excitation caused by L-DOPA was accompanied by afferent overload [5]. The dynamics of trace processes that outpace excitation remains unclear under conditions of dopamine-related disorders. The dynamics of EP analogs allows one to monitor these processes in various brain divisions, including the analyzing and extrapyramidal structures. This is particularly important for the early, symptom-free stages of dopamine-related disorders since it is reasonable to expect that it will be reflected by the dynamics of EP analogs.

Our objective was to find out how trace processes are related to contralateral changes in dopamine metabolism. Bearing in mind the postulate that brain functions are associated with preservation of the traces of previous processes in brain structures, the identification of the early manifestations of

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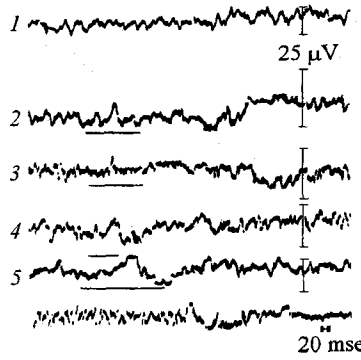

Fig. 1. Evoked potential analogs of simple configuration in different brain structures after the 10th injection of haloperidol. Here and in Figs. 2 and 3: *1)* visual cortex (field O2), *2)* caudate nucleus; *3)* adjacent nucleus; *4)* globus pallidus; *5)* motor cortex (field Prc1).

dopamine-related dysbalance is of both theoretical and practical importance.

MATERIALS AND METHODS

Experiments were performed on 5 dogs with chronically inserted electrodes in the visual (field O2) and motor (field Prc1) zones of the cortex, in the caudate nucleus (Cd), globus pallidus (GP), and the adjacent nucleus (Acc).

A motor reflex was conditioned in all the dogs. Six flashes of light (frequency 2 Hz) were followed by suprathreshold electrical stimulation of the forepaw (pulse duration 0.1 sec).

Dopamine hypo- and hyperfunction were modeled by chronic administration of haloperidol and L-DOPA, respectively. The preparations were injected at the stage of reflex stabilization (rising of the paw before the electrical pulse) when the EP dynamics in these brain structures acquired typical configuration [5]. Haloperidol was injected intramuscularly in a dose of 0.3 mg/kg every day until bradykinesia was attained, L-DOPA was administered *per os* every day in a dose of 20 mg/kg until psychomotor excitation became observable.

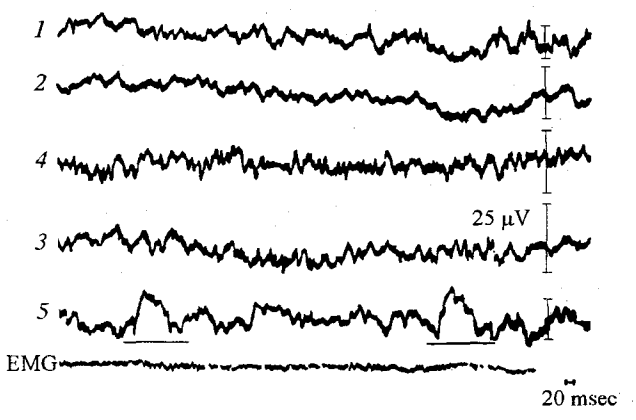

Fig. 2. Large-amplitude analogs of evoked potentials in the motor zone cortex coinciding with stimuli is rhythm. Here and in Fig. 3: *EMG)* electromyogram.

Changes in the location of EP analogs in the given brain structures, amplitudes, duration and configuration of the basic negative component (BNC) of EP analogs, and the relationships between EP analogs and motor reactions were analyzed against the background of haloperidol and L-DOPA. The major tendencies in the dynamics amplitude and temporal parameters of EP were expressed as the mean value and variation coefficient (W%) [3].

Since changes in BNC amplitude and duration were unilateral, numerical values are given only for the amplitude.

RESULTS

The stabilization stage of the conditioned defense reflex was characterized by the following regularities [1,5]: the percentage of correct responses per experiment was 60-70, BNC of EP and EP analogs acquired sustained M-configuration, the mean value and amplitude variability of EP analog BNC in the motor cortex increased from 12.5 (W%=14.1) to 31.6 μV (W%=25.9), in the visual zone both parameters decreased from 45.2 (W%=27) to 12.5 μV (W%=14.1), in subcortical structures the amplitude of BNC decreased, but remained variable, in the caudate nucleus it decreased from 22.1 (W%=26.9) to 14.8 μV (W%=27), in the globus pallidus from 35.4 (W%=36.7) to 19.3 μV (W%=30), and in the adjacent nucleus from 28.3 (W%=28) to 16.3 μV (W%=27). The location of EP analogs stabilized: they were confined to the motor zone of the cortex and to the subcortical structures. Generally, EP analogs accompanied motor reactions.

The following changes were observed after 7-11 injections of haloperidol: the configuration of the BNC of EP analogs became simple and similar in all studied brain structures (Fig. 1), M-configuration disappeared: the parameters of EP analogs were not affected by motor reactions. The mean value and variability of the BNC amplitude in the motor zone decreased to 23.6 μV (W%=13), in the other brain structures it remained at this level, but the variability coefficient decreased: in visual cortex to 12.9 μV (W%=12), in the caudate nucleus to 15.7 μV (W%=19.6), in the globus pallidus to 17.7 μV (W%=12.4), in the adjacent nucleus to 18.3 μV (W%=10.2).

Thus, haloperidol decreases the parameters and simplifies the configuration of EP analogs, particularly in the subcortical structures; all variants of M-configuration, which are formed by afferentations from the organs executing the motor reaction, dis-

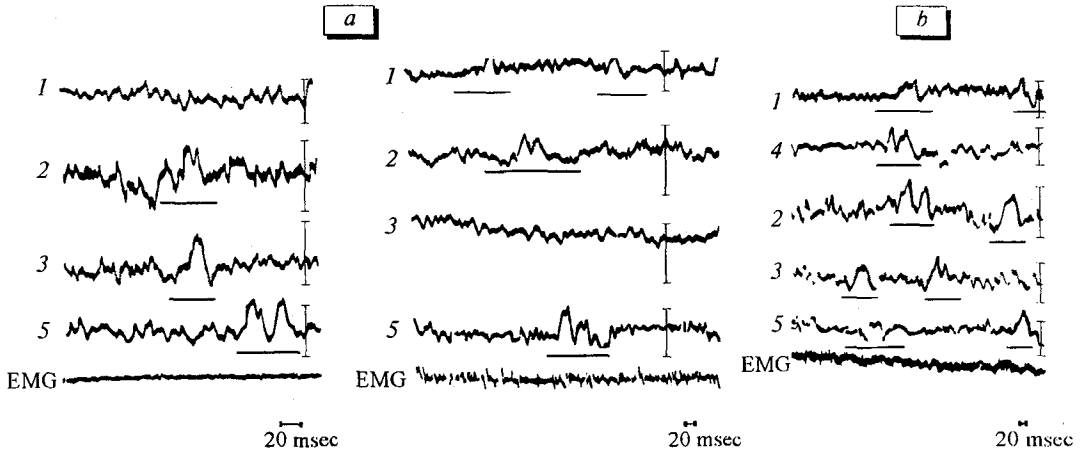

Fig. 3. Evoked potential analogs with simple and M-configuration the 4th injection of L-DOPA *(a)* and analogs with different configurations recorded in the same brain structure *(b)*.

appear. This indicates that the deficiency of motor afferentations occurs at clinically latent, symptom-free stage of dopamine hypofunction.

After 20-30 injections of haloperidol, the mean value and variability of the BNC amplitude of EP analogs in the motor zone increased to 43.0 μV (W%=23.9) and the analogs show a tendency to follow the stimulus in the rhythm (Fig. 2). The amplitude of EP analog BNC did not change significantly in the other studied structures: in caudate nucleus 15 μV (W%=20.2), in globus pallidus 13.6 μV (W%=11.9), in adjacent nucleus 20.2 μV (W%=11.8), and in visual zone 14.1 μV (W%=15.3). The analogs of EP were recorded in the motor zone or in subcortical structures, although not simultaneously; later they occurred only in the motor zone, which coincides with bradykinesia. It is noteworthy that EP analogs of simplified configuration were preserved in subcortical structures for a certain time period. In intact animals they were generally recorded at the beginning of training, when the motor reflex had not been conditioned. They are typical of the analyzing brain structures and reticular formation (outpacing integration of the sensor type) [6]. After several injections of haloperidol, EP analogs with a simple configuration were recorded in all studied brain structures, including basal ganglia, i. e., abundant structures were involved in the sensor type outpacing integration. Then this integration disappeared, and only EP analogs an extremely high amplitude remained in the motor zone as bradykinesia develops. Thus, the possibility that intense formation and reproduction of traces in the motor zone represent a compensatory process cannot ruled out.

Chronic administration of L-DOPA caused the following changes: the mean amplitude and variability of EP analog BNC increased in all studied brain structures: in the visual cortex to 36.4 μV (W%=27.6), in the caudate nucleus to 20.7 μV (W%=22.9), in the globus pallidus to 21.8 μV (W%=29), in the adjacent nucleus to 38.7 μV (W%=16.9), in the motor cortex to 29 μV (W%=25). The EP analogs of simple and M-configuration were recorded simultaneously: first in different structures (simple analogs in the visual zone and adjacent nucleus, analogs with M-configuration in the motor zone cortex and basal ganglia) (Fig. 3, *a*), then in all the structures (both analyzing and motor, Fig. 3, *b*); strong emotional reactions (unmotivated aggression) were observed only against this background.

Thus, the development of dopamine-related hyperfunction also starts from distortions in the trace processes. During stabilization of conditioned motor reflex EP analogs of M-configuration were observed in 80% of intact animals. Against the background of L-DOPA the occurrence of EP analogs with simple configuration was similar to that of EP-analogs with M-configuration which did not always coincide with the motor response. Against the background of L-DOPA EP analogs of simple and M-configuration, which were not always related to motor reaction, were recorded with equal probability.

The occurrence of EP analogs with M-configuration in the analyzing brain structures indicates increased sensitivity of these structures to afferentations from the organs involved in the motor reaction [6]. After the first injections of L-DOPA each structure reproduces the traces which are most adequate to its afferentations, which results in different locations of EP analogs with simple and complex configuration. At this stage of the of pathological integration behavioral changes were not observed. Chronic administration of introduction L-DOPA the

process of multisensor convergence loses its structural specificity: EP analogs with simple and complex configuration are recorded in the same structure. The relationship between EP analogs with M-configuration and motor reactions is lost. The degree of afferent overload of integration is sufficient for the development of psychomotor excitation.

Hyper-reactivity of brain structures caused by L-DOPA may be an important mechanism of psychopathology, namely, inability to select the significant stimuli from information flow [6-8]. Trace processes are the first to be affected.

Thus, a common principle has been discovered in contralateral shifts in dopamine metabolism: impairment of trace processes, outpacing excitations, and, consequently, of probabilistic prediction. It is noteworthy that specific changes in the afferent structure of trace processes occur long before the appearance of pathological symptoms.

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