Intercentral Relations under the Effect of Atypical and Typical Neuroleptics

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Chronic injections of haloperidol and sulpiride to dogs synchronized processes in the basal ganglia and visual analyzer, which may be explained by therapeutic effect of the neuroleptics. Haloperidol destroyed interaction between basal ganglia and motor cortex. Under the effect of sulpiride, the sensory tuning was observed not only in the basal ganglia, but also in the hippocampus.

Key Words: *haloperidol; sulpiride; intercentral relations*

Long-term treatment with typical neuroleptics is associated with the risk of drug-induced parkinsonism [1,2,6]. By contrast, atypical neuroleptics induce no extrapyramidal complications. The differences in the effect of typical and atypical neuroleptics at the receptor level are studied in details [6,10-13,16]. Our aim was to compare their systemic effects and to reveal functional relations between various cerebral structures under long-term treatment with haloperidol and sulpiride.

MATERIALS AND METHODS

Avoidance reaction was conditioned in 4 dogs with electrodes chronically implanted into the visual (field O_2) and motor (field Prc_1) cortical areas, caudate nucleus, globus pallidus, nucleus accumbens, and hippocampus. The signal stimuli (6 light flashes given at 2 Hz) were reinforced by suprathreshold electrical stimulation (0.1 sec pulse duration) of a forepaw between the 5th and 6th flashes.

Both EEC and evoked potentials (EP) were recorded during conditioning. The dynamics of the functional state of the brain structures was assessed by changes in the localization and parameters of EP induced by the flash stimulation: configuration, amplitude, and duration of the major negative component [4].

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The drugs were injected after stabilization of motor skills. In two dogs, haloperidol was administered intramuscularly in a daily dose of 0.3 mg/kg during 40-50 days, and after a 2-month interval sulpiride was injected intramuscularly in a daily dose of 5 mg/kg during 40-50 days. Other two dogs were treated with sulpiride and after a 2-month interval with haloperidol.

RESULTS

At the beginning of conditioning, the visual cortex was the leading element of central integration. In this region EP were recorded systematically, although their shape, amplitude, and duration varied. EP in the caudate nucleus had predominantly a simple shape (Fig. 1, *a*) and short latency (20-25 msec). The short-latency EP arose synchronously in the caudate nucleus and visual cortex. Their dynamics was of the same direction, which was considered as a sign of sensory tuning of the basal ganglia (BG) [3,4]. Periodically, long-latency (35-40 msec) M-shaped EP appeared in the caudate nucleus: initially, when flash coincided with the movement, and then in response to the first flash in the series (Fig. 1, *b*). This succession indicates that afferentation induced by motor response plays an important role in the genesis of M-shaped EP [7,8]. EP were rarely observed in the motor cortex. During conditioning, the shape of EP in the nucleus accumbens and globus pallidus became more complex: additional negative waves appeared (Fig. 1, *c*). In the hippo-

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campus the shape of EP had a number of variants. One of them is of particular importance, because it never occurred when the flash coincided with the movement (Fig. 2, *a*). The main prerequisite of such EP shape was the absence of afferentation induced by movement (motor-negative EP).

After stabilization of the motor skill, the functional activity was shifted to the integrative-triggering structures: in the motor cortex the number of EP, their amplitude, and duration increased, their latency decreased, and the shape became more complex. In contrast, in the visual cortex the amplitude-temporal parameters of EP decreased and stabilized. The long-latency M-shaped EP predominated in the caudate nucleus. The shape of EP remained complex in the nucleus accumbens and globus pallidus. Motor-negative EP disappeared in hippocampus.

Haloperidol was administered after stabilization of the motor skill. It was shown that therapeutic effect of haloperidol manifested 1-2 weeks after the start of treatment due to compensatory intensification of the dopamine metabolism [6]. The same latency characterized the rearrangement of the intercentral relations: the dynamics of EP typical of the stage of skill stabilization changed after 12-14-day administration of haloperidol [7,8]. EP disappeared in the motor cortex. Short-latency EP of a similar simple shape appeared synchronously in the visual cortex and subcortical structures (Fig. 1, *d*). The latency of EP in the subcortical structures decreased and became similar: 26.8 msec in the caudate nucleus, 27.5 msec in the globus pallidus, and 26.8 msec in the nucleus accumbens. Therefore, the intact dogs demonstrated sensory tuning in the caudate nucleus, while under the effect of haloperidol the tuning took place in the caudate nucleus, globus pallidus, and nucleus accumbens. Presumably, this variant of integration underlies the therapeutic effect of haloperidol. Psychic disorders related to hyperfunction of the dopaminergic systems are accompanied by disturbance of the choice of meaningful stimuli [14]. It cannot be ruled out that functional synchronization in the visual cortex and BG changes the perceptive processes toward more strict selectivity.

After 4-6-week administration of haloperidol the symptoms of bradykinesia appeared and were manifested in general constraint and motor slowdown. In this period the dynamics of EP in the motor cortex differed from that in intact dogs: the amplitude and duration of EP drastically increased, while their latency was prolonged, and the shape became simple. Numerous high-amplitude EP analogs were recorded during the interstimulus intervals (Fig. 1, *e*). The motor-negative EP arose again and dominated in the hippocampus (Fig. 2, *b*), which attests to restriction of the motion-induced afferent influences.

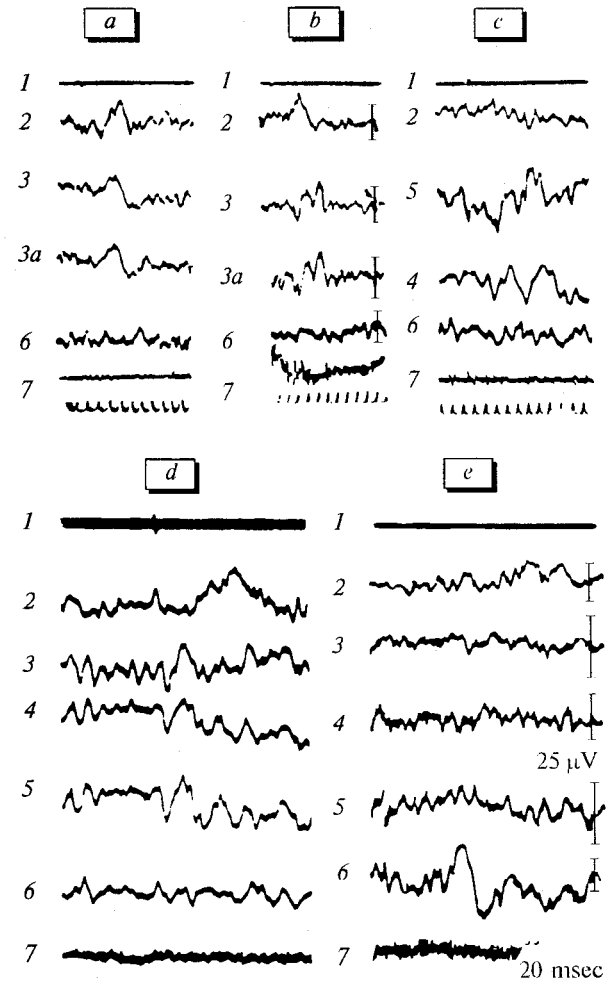

Fig. 1. Configuration of potentials evoked by light flashes in various cerebral structures in dogs. *a*) start of conditioning (24th presentation of flashes with reinforcement); *b*) and *c*) active conditioning (105th and 137th presentation, respectively); *d*) after 14-16-day haloperidol treatment; *e*) after 25-day haloperidol treatment. *1*) stimulation marks; *2*) visual cortex; *3*) and *3a*) caudate nucleus (2 combinations of 3 electrodes implanted into the structure); *4*) globus pallidus; *5*) nucleus accumbens; *6*) motor cortex; *7*) electromyogram of forepaw.

It was shown that the corticospinal pathway is functionally intact in parkinsonism [9], i.e. the main efferent channel of integration is preserved. Hence, the processes in the motor cortex can be distorted due to disturbances in the afferent traffic. If BG is the sensor analyzer for the motor system [14,17], this function in the haloperidol-treated dogs is performed under conditions of deficient motion-induced afferentation. Presumably, atypical processes in the motor cortex reflected another tentative mechanism of bradykinesia — transfer of motor automaticity to the cortical level [15].

Chronic injections of sulpiride induced no bradykinesia. There were no distortions of the processes in the motor cortex: after 4-6-week treatment, the short-latency EP of a complex shape were recorded.

At the same time, we observed the same (as with haloperidol) effect of unified sensory tuning in BG:

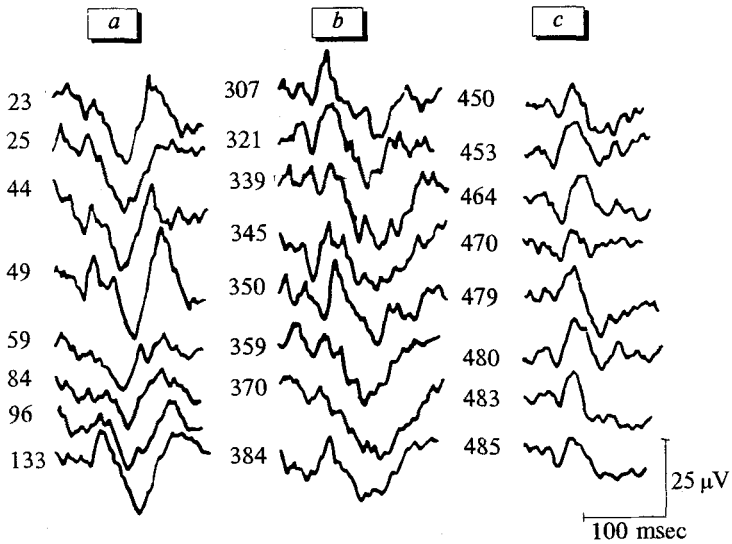

Fig. 2. Configuration of evoked potentials in dog hippocampus. *a*) in the absence of conditioned withdrawal of forepaw; against the background of chronic treatment with haloperidol (*b*) or sulpiride (*c*). Figures show the number of presentation of the stimulus with reinforcement.

the latency of EP decreased and became practically identical in all structures (25.4 msec in the caudate nucleus, 28.5 msec in the globus pallidus, and 27.5 msec in the nucleus accumbens), the EP shape became simple, EP in the visual cortex and subcortical structures appeared synchronously. However, in contrast to haloperidol, sulpiride did not restore variability of EP parameters in the visual cortex. The long-latency M-shaped EP persisted in the BG against the background of sulpiride effect. They appeared episodically simultaneously with EP in the motor cortex. Thus, in intact dogs the functional connections "BG — visual analyzer" and "BG — motor cortex" appeared successively at various stage of conditioning, while in the sulpiride-treated dogs they arose simultaneously.

It might be conjectured that sulpiride does not restrict the motion-induced afferentation: the M-shaped EP persist in BG. This is also confirmed by principle differences in the dynamics of EP in the hippocampus under conditions of chronic treatment with haloperidol and sulpiride. In the haloperidol-treated dogs the motor-negative EP predominate in the hippocampus, while in sulpiride-treated animals only the early component of EP is preserved, and these EP are recorded synchronously with EP in the BG (Fig. 2, *c*).

Therefore, synchronization of the processes in the BG and visual analyzer is a common effect of haloperidol and sulpiride. It cannot be ruled out, that this mechanism is related to the therapeutic effect of both typical and atypical neuroleptics. On the other hand, these drugs disturb other functional connections. Haloperidol restricts the motion-induced afferentation and disturbs the interaction between BG and the motor cortex. Sulpiride induces sensory tuning not only in the BG, but also in the hippocampus (structures of the limbic system). It should be noted that haloperidol is efficient in psychomotor excitation, while sulpiride is effective in states accompanied by slowdown and adynamia [1,6].

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