GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Electrical Activity in the Structures of the Caudate-Putamen Complex in Experimental Depressive Syndrome

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Electrical activity of rat brain was modified by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine administered according to a scheme inducing experimental depressive syndrome. The changes were manifested by local epileptiform activity in the structures of the caudate-putamen complex, an increase in the δ-rhythm power, and a decrease in the α-rhythm power, which attests to hyperactivity in these structures. An increase in the δ-rhythm power was observed in the hippocamp.

Key Words: *electrical activity; caudate-putamen complex; MPTP; depressive syndrome; rats*

We have developed a rat model of depressive syndrome (DS) provoked by repeated systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [6]. Rats treated with MPTP according to the proposed scheme developed a stable state of reduced motivation activity combined with agedonia and behavioral despair, which made it possible to define these behavioral changes as DS. The rats demonstrated characteristic disorders of REM sleep similar to those occurring in patients with endogenous depression [4].

The striatal mechanisms are involved in the realization of highest psychical functions [7]. Electrical stimulation of striatal structures inhibits motor activity and provokes behavioral depression in animals [1,8,13].

Our aim was to study changes in electrical activity (EA) developing in the structures of the striatal caudate-putamen complex (CPC), hippocamp, and cerebral cortex in rats treated with MPTP according to the scheme inducing experimental DS.

MATERIALS AND METHODS

The study was carried out on 19 random-bred male Wistar rats with the initial weight 270-330 g. The animals were maintained under standard vivarium conditions with the natural lighting schedule, 2 rats per cage, and had free access to food and water. Under chloral hydrate anesthesia (400 mg/kg intraperitoneally) insulated Nichrome electrodes 200 μ in diameter were implanted into the rostral part of the CPC of the left hemisphere and into the dorsal hippocamp of the right hemisphere according to stereotaxic coordinates [14], and a ball-type silver electrode was installed in the area of the right sensorimotor cortex. To record EA of the cervical muscles, Nichrome electrodes 200 μ in diameter with a noninsulated tip were implanted into the muscles. Monopolar recording from the brain and bipolar recording from the cervical muscles were performed in unrestrained animals with an EEG-

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4314F electroencephalograph (Nihon Kohden). Primary recordings were made continuously for 4 h in the same day time starting from postoperative days 5 or 6. On the following day after primary recording of cerebral EA, administration of MPTP (20 mg/kg) was started in the experimental group (n=9), while the control group (n=10) was treated with physiological saline. MPTP (synthesized at the Institute of Pharmacology, Moscow) was dissolved in physiological saline immediately before injection. MPTP and saline were injected intraperitoneally every day in a volume of 1 ml/kg body weight for 12 days. The subsequent recordings of cerebral EA was performed both in the period of treatment with MPTP on days 3-4 after the beginning of administration (the stage of DS formation), on days 11-12 (the stage of marked depression), and one week after discontinuation of the drug (the stage of restoration of behavioral activity in the MPTP-treated group). During terminal 10-min period of each recording, EA of the brain was also recorded with a TEAC MR-30 tape recorder. The spectral power was calculated with the fast Fourrier transform algorithm in the range of 1-64 Hz (1 Hz bin) using an RTI-820 analog-digital converter. The epoch of analysis was 4 sec. Eight to twelve epochs from each structure of every rat were averaged. The power of EA was determined in the following physiological frequency ranges: δ_1 (0-2 Hz), δ_2 (2-4 Hz), θ_1 (4-6 Hz), θ_2 (6-8 Hz), α (8-13 Hz), β_1 (14-19 Hz), and β_2 (20-30 Hz). For each record from a cerebral structure in the experimental and control groups the mean spectral power was determined in the specified frequency ranges. The secondary statistical analysis was performed using Student's unpaired parametric t test and dispersion analysis for the repeated measurements (Repeated Measures ANOVA) with subsequent comparison of the mean values of the dispersion complex according to Tukey's t_Q test (Primer software). At the end of experiments, the macroscopic morphological control of subcortical localization of the electrodes was performed.

RESULTS

In 6 out of 9 rats injected with MPTP, the epileptiform activity was recorded in CPC structures during the treatment period and during the first week after discontinuation of the drug which corresponds to the period of behavioral depression in rats [6]. In other 3 rats the epileptiform activity was not documented during the recording period. The periods of local epileptiform activity were observed in wakeful rats: they often occurred after external manipulations such as transfer of the rats into experimental cage, connection of the electrodes, etc., and lasted for 2-50 min. The amplitude of epileptiform discharges (spikes or sharp waves) was 200-400 μV, and their frequency varied during a single recording period from 0.2 to 0.7 sec^{-1} (Fig. 1). In some cases the epileptiform activity spread to hippocampal regions and sensorimotor cortex, and the frequency of generalized discharges was 1-4 sec^{-1}. Both local and generalized epileptiform activity were not accompanied by marked seizures. In control rats no changes were observed in electrical activity and behavior.

At the stage of DS formation in MPTP-treated rats, the power of EA increased in the δ_1-range compared with the control value (respectively, 11.7±2.3 and 4.1±0.9%, p<0.01, Fig. 2, *b*). The increase in the spectral density in this range was also observed one week after discontinuation of MPTP (9.2±1.1 and 4.6±0.8%, respectively, p<0.01, Fig. 2, *d*). At the stages of marked behavioral depression

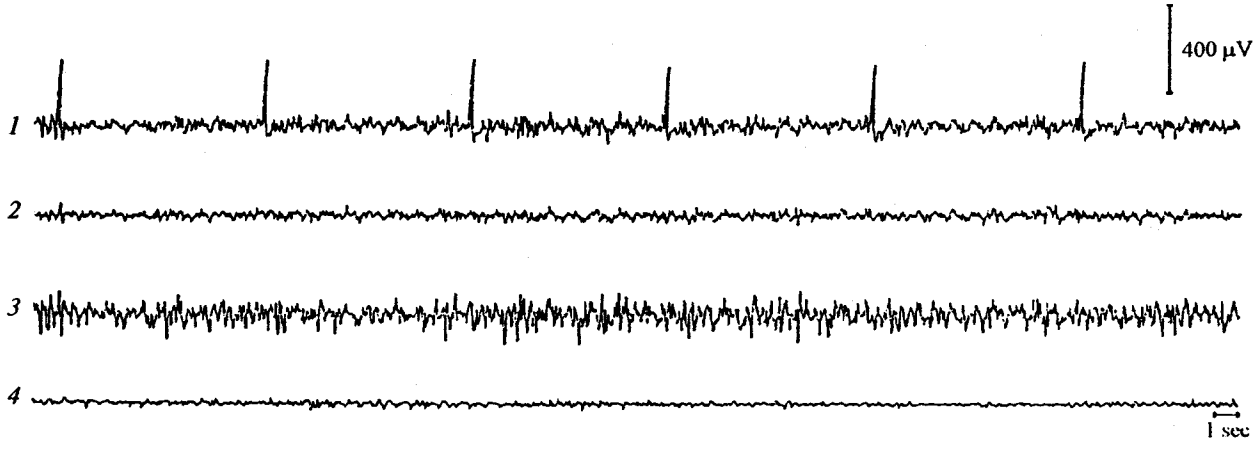

Fig. 1. Electrical activity of rat cerebral structures under the effect of MPTP. *1*) rostral subdivision of the caudate-putamen complex in the left hemisphere; *2*) sensorimotor cortex of the right hemisphere; *3*) dorsal hippocamp of the right hemisphere; *4*) myogram of cervical muscles.

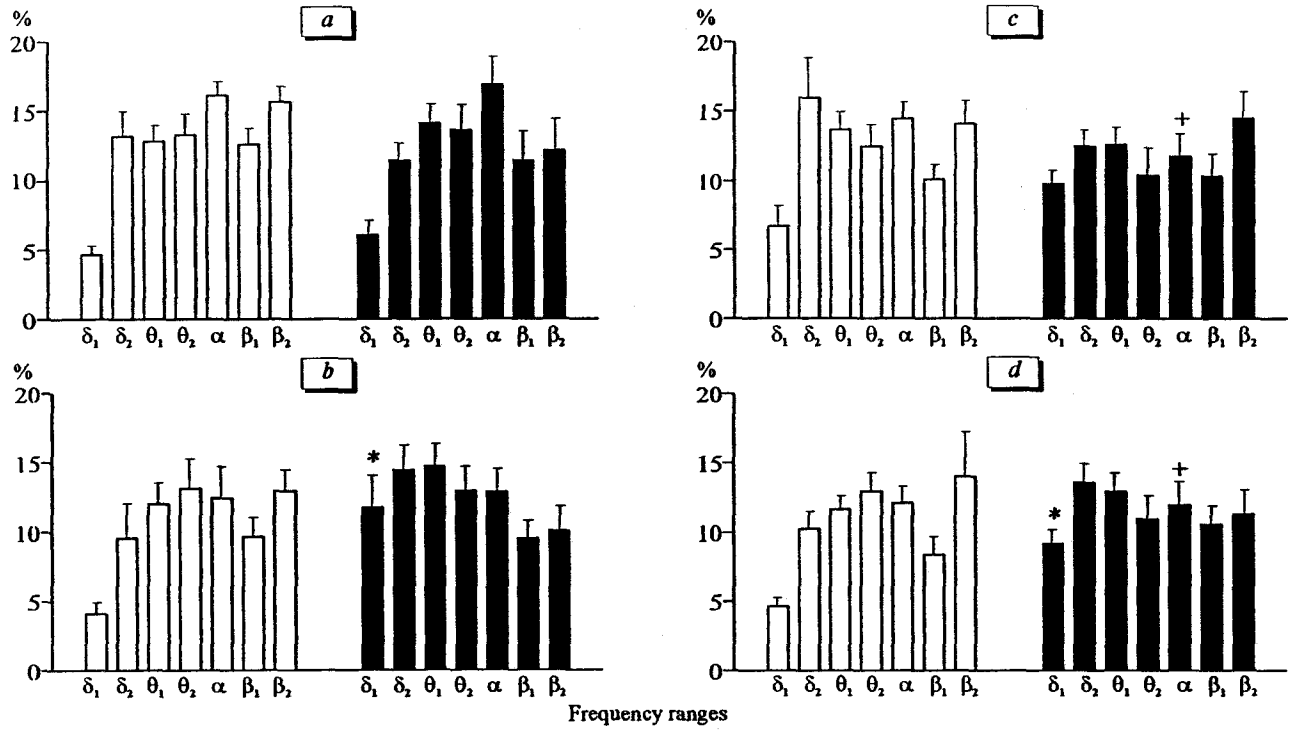

Fig. 2. Spectral power histograms of electrical activity in the structures of the caudate-putamen complex in rats treated with MPTP (solid bars) or control physiological saline (white bars). *a*) prior to injection; *b*) on days 3-4 of treatment (depressive syndrome formation induced by MPTP); *c*) on days 11-12 of treatment (marked depression provoked by MPTP); *d*) 1 week after discontinuation of MPTP (restoration of behavioral activity in MPTP-treated animals). Ordinates: spectral power. *$p<0.01$ in comparison with the control animals treated with physiological saline (Student's unpaired parametric *t* test); +$p<0.05$ in comparison with the respective initial value of spectral power in this group treated with MPTP (Tukey's t_Q test).

and restoration of behavioral activity, a decrease in the rhythmic activity of CPC structures was observed in MPTP-treated rats in the α-frequency range [$F(3,15)= 5.08$, $p<0.05$]: the spectral power of EA in this range was lower than the initial value (t_Q=4.82 and 4.64, respectively; in both cases $p<0.05$, Fig. 2, *a-d*).

At the stage of DS formation, the hippocampal δ_1-rhythm power in MPTP-treated rats was higher in comparison with the rats treated with physiological saline (6.7±1.1 and 3.4±0.3%, respectively; $p<0.05$).

In all ranges of physiological frequencies or period of observation there were no significant changes in the EA in the sensorimotor cortex of MPTP-treated rats in comparison with the corresponding values in control group or with the initial values in the experimental group.

There were no changes of spectral power in any studied cerebral structure in the control rats treated with physiological saline.

The local epileptiform activity in CPC of MPTP-treated rats was detected at all stages of DS development. At the stages of marked behavioral depression and restoration of behavioral activity, these rats were characterized by a decrease in the α-rhythm power in CPC. In clinic, a decrease of the α-rhythm power in the cortex of the patients with endogenous depression is considered as a sign of activation of this structure [12]. In experimental physiology, the state of localized tonic excitation in the brain is considered to be related to a decrease in the α-rhythm power. Therefore, the decrease in the α-rhythm power in CPC found in our work attests to hyperactivation of this cerebral subdivision, which corresponds to continuation of the depressive state in rats.

The observed increase of the δ-rhythm power, which occurred predominantly in the CPC structures, may indicate their tonic excitation, because the EA increase in the δ-frequency range indicates tonic excitation of the dominant foci [9,10]. Emotional stress of any sign is characterized by a low-frequency synchronized activity (δ- and θ-rhythms) of the cortex and subcortical cerebral structures, which is a form of the "activation reaction" [3]. Animal experiments showed that the δ-rhythm correlates with negative emotional states [3]. Enhancement of synchronization and slowing of rhythmicity were observed in the caudate nuclei and other cerebral structures in rabbits within the framework of the "reserpine depression" model [2].

Taken together, the changes in cerebral EA (the epileptiform activity, a decrease in the α-rhythm power, and an increase in the δ-rhythm power in the CPC structures) attest to hyperactivation of CPC in the model of experimental depression induced by systemic administration of MPTP. The hyperactive structures in CPC may act as a pathological determinant that forms the pathological system of the depressive syndrome that incorporates a number of cerebral structures [5]. This determinant activates the emotionally negative zones, and the activated state is maintained by the excited hippocamp which is known to be involved in emotional behavior [11] and which has a modified EA with increment of the δ-rhythm power at the stage of DS formation. The possibility that pathological system of this syndrome incorporates some structures in the neocortex, where significant changes could be revealed by aggravating the experimental depressive state, cannot be excluded.

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REFERENCES

1. E. B. Arushanyan and L. V. Shishlyannikova, *Zh. Vyssh. Nerv. Deyat.*, No. 1, 80-87 (1979).
2. T. A. Zamoshchina and A. S. Saratikov, *Zh. Nevropatol. Psikhiatr.*, **84**, No. 9, 1362-1367 (1984).
3. L. R. Kvirkveliya, in: *Hippocampal Electrical Activity and Behavior* [in Russian], Tbilisi (1984), pp. 59-95.
4. N. A. Krupina, G. N. Kryzhanovskii, T. E. Iordanskaya *et al., Byull. Eksp. Biol. Med.*, **123**, No. 2, 138-142 (1997).
5. G. N. Kryzhanovskii, *Zh. Nevropatol. Psikhiatr.*, **96**, No. 6, 5-11 (1996).
6. G. N. Kryzhanovskii, N. A. Krupina, and V. G. Kucheryanu, *Zh. Vyssh. Nerv. Deyat.*, **45**, No. 2, 377-387 (1995).
7. I. P. Lukashevich and S. B. Buklina, *Ibid.*, **46**, No. 1, 49-54 (1996).
8. V. A. Otellin and E. B. Arushanyan, in: *Nigro-Strionigral System* [in Russian], Moscow (1998), pp. 103-169.
9. R. A. Pavlygina, Yu. V. Lyubimova, and V. I. Davydov, *Zh. Vyssh. Nerv. Deyat.*, **41**, No. 1, 122-130 (1991).
10. G. Ya. Roshchina, *Ibid.*, **45**, No. 6, 1167-1173 (1995).
11. P. V. Simonov, *Emotional Brain* [in Russian], Moscow (1981).
12. V. B. Strelets, A. M. Ivanitskii, and G. A. Ivanitskii *et al., Zh. Vyssh. Nerv. Deyat.*, **46**, No. 2, 274-281 (1996).
13. K. B. Shapovalova, *Fiziol. Zh. SSSR*, **71**, No. 5, 537-553 (1985).
14. G. Paxinos and C. Watson, *The Rat Brain Coordinates*, New York (1982).