EFFECT OF PHENYTOIN SODIUM ON AN EXPERIMENTAL PARKINSONIAN SYNDROME

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A basic condition of the development of Parkinsonism is dopamine (DA) deficiency in the caudate nuclei (CN). If dopamine deficiency in CN is present, disinhibition and hyperactivation of cholinergic neurons take place, with the result that a generator of pathologically enhanced excitation (GPEE) is formed in CN [2]. The Parkinsonian syndrome induced by injection of tetanus toxin [1], kainic acid [3], acetylcholine [7], and antibodies to DA [5] into CN has been shown to be linked with GPEE formation in CN. Systemic injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which damages DA neurons of the substantia nigra, induces various types of Parkinsonian syndrome in animals [8, 13]. This effect is due to the end product of oxidation of MPTP, namely 1-methyl-4-phenylpyridinium (MPP^+) [9, 11]. The writers have shown that the Parkinsonian syndrome induced by systemic administration of MPTP and intranigral injection of MPP^+ also is linked with GPEE formation in CN [4, 6]. We have postulated that anticonvulsants suppressing the GPEE in CN may weaken the Parkinsonian syndrome.

The aim of this investigation was to study the effect of phenytoin sodium, which is widely used as an antiepileptic agent, on the electrophysiological and clinical manifestations of the Parkinsonian syndrome induced by systemic administration of MPTP.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male rats aged 12 months and weighing 500-650 g. A model of a Parkinsonian syndrome was created by intraperitoneal injection of MPTP hydrochloride into the animals in a dose of 20 mg/kg for 6 days at intervals of 12 h (the total dose of the neurotoxin was 240 mg/kg). Animals of the control group received an injection of the corresponding volume of physiological saline. The animals were kept in individual cages under standard animal house conditions and on an ordinary diet. Oligokinesia, rigidity, and tremor were assessed on a point system [5]. To record electrical activity (EA) silver ball electrodes were implanted on the surface of the sensomotor cortex (SMC) of the animals anesthetized with hexobarbital, and nichrome electrodes were inserted into the rostral zones of CN. The electrical activity of SMC and CN was recorded in unrestrained animals before injection of MPTP and against the background of extrapyramidal symptoms. Phenytoin sodium in a dose of 20 mg/kg was injected intraperitoneally into animals which exhibited a marked Parkinsonian syndrome. Physiological saline was injected in the same volume into animals of the control group with a Parkinsonian syndrome. EA of the cortex and CN, parameters of oligokinesia, rigidity, and tremor were recorded in the animals before and in the course of 4-6 h after injection of phenytoin sodium. The experimental results were subjected to statistical analysis.

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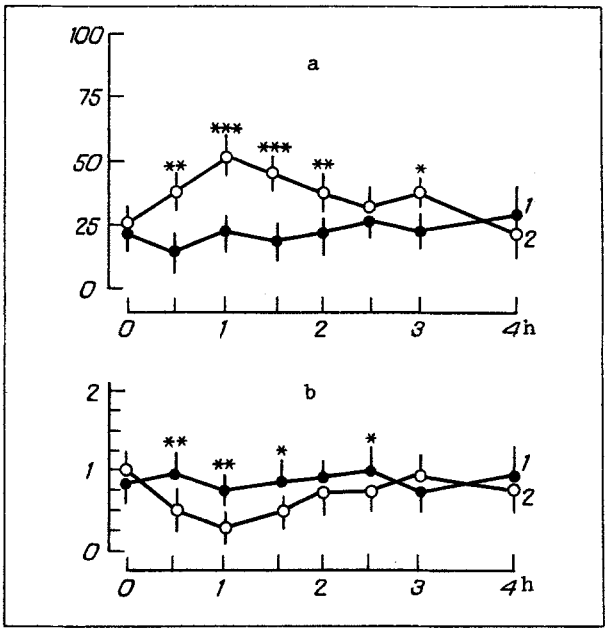

Fig. 1. Effect of phenytoin sodium on oligokinesia and rigidity induced by systemic injection of MPTP. Vertical axis: a) motor activity (in per cent, number of squares crossed and number of rearings by intact animals taken as 100%), b) rigidity (in points). Horizontal axis, time of observation (in h) after injection of phenytoin sodium. 1) Intensity of phenomena in control animals (injection of physiological saline), 2) in experimental animals (injection of phenytoin sodium). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with control at same period of observation.

EXPERIMENTAL RESULTS

Marked bradykinesia, in the form of slowing of movements, and oligokinesia, or a marked reduction in the quantity and quality of different types of motor activity (a sharp decrease in the number of squares crossed in the open field test, disappearance of rearing, of investigative activity, and grooming) were observed in most (32 or 44) animals 6-8 days after the beginning of injection of MPTP. Rigidity of the muscles in these animals was less marked (1 point). Transient and low-amplitude tremor of the head was observed in one-third of the experimental animals (14 of 44). Besides the motor disturbances, reduction of body weight, hypothermia, and various autonomic disturbances were recorded in the majority of animals.

Systemic injection of phenytoin sodium caused an increase in motor activity of most (13 of 18) animals with a Parkinsonian syndrome (Fig. 1a). This effect was recorded 20-30 min after injection of the drug and it was most marked for 1-1.5 h. Later the animals' locomotor activity was depressed. A second, but smaller increase in motor activity was observed 3 h after injection of phenytoin sodium.

Under the influence of phenytoin sodium rigidity was also reduced, and this effect was observed 1-1.5 h after injection of the drug and continued until 2.5 h. The effect of phenytoin sodium on rigidity was less marked than on oligokinesia (Fig. 1b).

Spontaneous (before injection of MPTP) EA in CN and SMC was characterized by dysrhythmia, and by the presence of low-amplitude (40-60 μV) fast and slow waves with a periodic thera-like component (Fig. 2a). In animals with marked oligokinesia and rigidity 6-8 days after the beginning of MPTP injections paroxysmal discharges of high-amplitude fast and slow waves were recorded in CN and SMC. EA recorded from both structures revealed grouped high-amplitude slow waves with a frequency of 0.5-1 Hz and an amplitude of over 300 μV. These changes in EA were more marked in CN, in which the amplitude of the slow wave reached 600 μV (Fig. 2b).

Changes in EA in SMC and CN appeared 30-40 min after injection of phenytoin sodium and took the form of suppression of high-amplitude paroxysmal activity. A decrease in the number and duration of paroxysmal discharges and in the amplitude of the slow and fast waves was noted. Irregular fast activity against a background of diffuse slow waves was recorded in CN

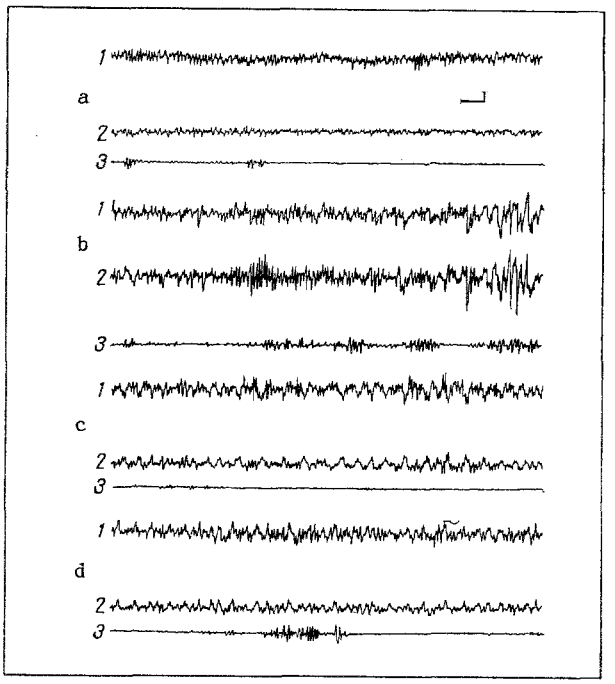

Fig. 2. EA recorded in SMC (1) and CN (2) and tremor (3) recorded before (a) and on 7th day after (b) beginning of injection of MPTP, in the presence of clinically marked oligokinesia, rigidity, and low-amplitude tremor of the head; c and d) the same parameters of the same rat 1 and 3 h respectively after intraperitoneal injection of 20 mg/kg phenytoin sodium. Calibration: 200 μV, 1 sec. Explanation in text.

1 h after injection of the drug. Meanwhile single pointed waves and slow activity of average amplitude (150-200 V) still remained in SMC (Fig. 2c). After 1.5 h the pointed waves disappeared and the amplitude of slow activity was reduced, while low-amplitude fast activity appeared in the cerebral cortex. Changes in EA recorded both in CN and in SMC lasted 3-3.5 h after injection of phenytoin sodium (Fig. 2d). EA in SMC and CN 4 h after injection of phenytoin sodium differed only a little from EA before injection of the drug.

In control experiments (6 animals) systemic injection of physiological saline had no significant effect either on electrical activity in SMC and CN or on the clinical manifestations of the Parkinsonian syndrome.

Comparison of changes in the clinical and electromyographic manifestations of the Parkinsonian syndrome after systemic administration of phenytoin sodium revealed correlation between these changes with time: suppression of paroxysmal activity began 30 min after injection of phenytoin sodium and was most marked for a period of 1-1.5 h, coinciding with reduction of the extrapyramidal symptoms; restoration of paroxysmal electrical activity in CN and SMC 4 h after injection of the drug corresponded to the appearance of oligokinesia and rigidity. The effect of phenytoin sodium was exhibited primarily as suppression of paroxysmal activity in CN.

Thus systemic administration of phenytoin sodium suppresses the GPEE in CN. Suppression of the GPEE correlates with reduction of bradykinesia, oligokinesia, and rigidity. The results confirm that the formation of a generator of pathologically enhanced excitation in CN is the immediate pathogenetic mechanism of the Parkinsonian syndrome. On the basis of these results it can be concluded that the addition of phenytoin sodium to pathogenetic therapy may prove very effective in the treatment of Parkinsonism. It has recently been shown that anticonvulsants such as primidone and clonazepam are able to suppress tremor in patients with Parkinsonism [10, 12].

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EFFECT OF ADAPTATION TO SHORT-TERM STRESS ON RESISTANCE OF PARAMETERS OF MYOCARDIAL ENERGY METABOLISM AND CONTRACTILE FUNCTION TO ACUTE HYPOXIC HYPOXIA AND REOXYGENATION

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Adaptation to short-term stress regularly increases the resistance of the heart to ischemic and reperfusion arrhythmias [3] and limits depression of the contractile function and disturbances of the electrical stability of the heart in experimental myocardial infarction [8]. However, it has not yet been settled whether this protective effect is due purely to limitation of the stress reaction, which is always observed during adaptation to short-term stress [2], or whether this adaptation involves a direct increase in the resistance of the heart to acute hypoxia and subsequent reoxygenation.

The aim of this investigation was to assess the effect of preliminary adaptation to stress on the resistance of the parameters of the energy metabolism and contractile function of the heart to acute hypoxia and subsequent reoxygenation.

EXPERIMENTAL METHOD

The investigation was conducted on male Wistar rats weighing 200-250 g. Adaptation to stress was carried out by immobilizing the animals in the supine position for between 15 min and 1 h, 8 times at intervals of 1 day. Acute experiments were then carried out on the adapted and control animals, under pentobarbital anesthesia (50 mg/kg) and artificial respiration. The rats' hearts were frozen actually in the chest with Wollenberger's forceps: in the animals of group 1 in a state of relative physiological rest, in those of group 2 in a state of hypoxia (4 min after stopping artificial respiration), and in group 3 during reoxygenation (5 min after the resumption of respiration). The frozen hearts were used to determine the parameters of myocardial energy metabolism. ATP, ADP, AMP, and lactate were determined with the aid of kits from "Boehringer," and creatine

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