Repeated Haloperidol Microinjections to the Globus Pallidus Induce Vegetative Components of Parkinsonian Syndrome in Rats

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 125, No. 6, pp. 615-617, June, 1998
Original article submitted July 4, 1997

Experiments on rats show that repeated bilateral microinjections of haloperidiol (5 μg) into globus pallidus or caudal neostriaum impair conditioned passive avoidance reaction and do not affect spontaneous motor activity. Unlike haloperidol injections to the rostral neostriatum, chronic blockade of the pallidal dopamineric system induces vegetative and trophic disturbances.

Key Words: *dopaminergic system; haloperidol; striatum; globus pallidus; motor activity; vegetative disorders; conditioned avoidance reaction*

Reversible akinesia-rigidity syndrome, similar to motor disturbances in parkinsonism, has been previously reproduced in rats by repeated haloperidol injections into the neostriatum [4]. The basis for this phenomenon is disintegration of transmitter systems in the anterior neostriatum (caudate nucleus) [5,6]. Taking into account morphofunctional interrelations between the basal nuclei, it can be hypothesized that the dopaminergic system of the caudal neostriatum (CNS) and paleostriatum (globus pallidus, GP) is involved into the pathogenesis of parkinsonism. To verify this assumption we investigated the effects of repeated injections of the dopamine antagonist haloperidol to GP and CNS in rats. Experimental conditions, i.e., the procedure and regimen of microinjections (MI), dose of haloperidol, and behavioral tests were analogous to our previous experiments on rostral neostriatum [4-6].

MATERIALS AND METHODS

Experiments were carried out on 22 male Wistar rats weighing 250-300 g. The animals were trained active avoidance response in a shuttle box [5,6]. Polyethylene cannulas containing haloperidol or sterile apyrogenic physiological saline (control) were implanted to GP and CNS under Hexenal narcosis. Each experimental group consisted of 4-6 animals. Stereotactic coordinates for GP were 0.8-1.0 mm caudal to bregma, 1.8-2.8 lateral to the median scull line, and 7.0-7.5 mm ventral to skull surface, while for CNS the corresponding coordinates were 0.5-0.8, 1.0-1.5, and 6.0-6.5 mm, respectively. One microinjection contained 5 mg haloperidol in 0.5 μl. Procedure of microinjections was described previously [4]. Experiments were started 2-3 days postoperation. Haloperidol or physiological saline were injected daily for 3 weeks. Behavioral tests were performed 3 times per week at 1-2-day intervals: 15-20 min postinjection, spontaneous motor activity in an open field was assessed for 5 min and then the parameters of conditioned active avoidance were evaluated. The tests were continued 2-3 weeks after withdrawal of MI.

At the end of experiments the rats were sacrificed under Hexenal narcosis, and the location of implanted cannulas was verified. Only the data obtained on animals with precise bilateral localization of CNS and GP cannulas were taken into consideration and processed statistically by the Student *t* test.

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0007-4888/98/0006-0542$20.00

RESULTS

Microinjections of physiological saline to GP and CNS impaired the performance of active avoidance to 55-60% during the first week: in particular, on the 3rd day of MI to GP, correct responses constituted 57.1±14.8%, which significantly differ from the baseline value (p=0.02). However, during the second and third weeks of MI this parameter in control animals did not differ from the normal. The latency of avoidance reaction and spontaneous motor activity remained unaffected.

Haloperidol produced more pronounced behavioral effects which were observed primarily during the first 10-12 days of the experiment. The number of correct choices in rats injected into GP and CNS decreased to 20-25% and 40-45%, respectively. These shifts were significant only after the first MI, since similar changes were observed in control rats. Haloperidol injected into GP suppressed spontaneous motor activity (Fig. 1) and slightly shortened the latency of avoidance reaction (Fig. 2). No motor (muscular) disturbances were noted. In contrast to these observation, modulation of the dopaminergic system of the rostral neostriatum [4,5] induced rigidity of skeletal muscles and pronounced hypokinesis, which first appeared during the first few days of haloperidol treatment and peaked during the 2nd-3rd weeks (the absence of spontaneous motions). However, marked vegetative (dystrophic) disturbances such as wet, untidy, and ruffled hair, sanious nasal discharge, etc. were noted in animals injected with haloperidol into GP (but not CNS). These signs first appeared on 5-6 days of haloperidol treatment. Despite abundant and high quality nutrition, the rats lost weight. One animal died on day 17 of the experiment. Body weight and appearance of the rats returned to initial only 7-10 days after haloperidol withdrawal.

These experiments demonstrated that haloperidol MI into the neo- and paleostriatum induce similar neuropharmacological effects: impairment of conditioned avoidance reaction, suppression of motor activity, and reduction of adaptive capacity. Chronic blockade of neostriatal dopaminergic system induced primarily motor (muscular) disorders, while blockade

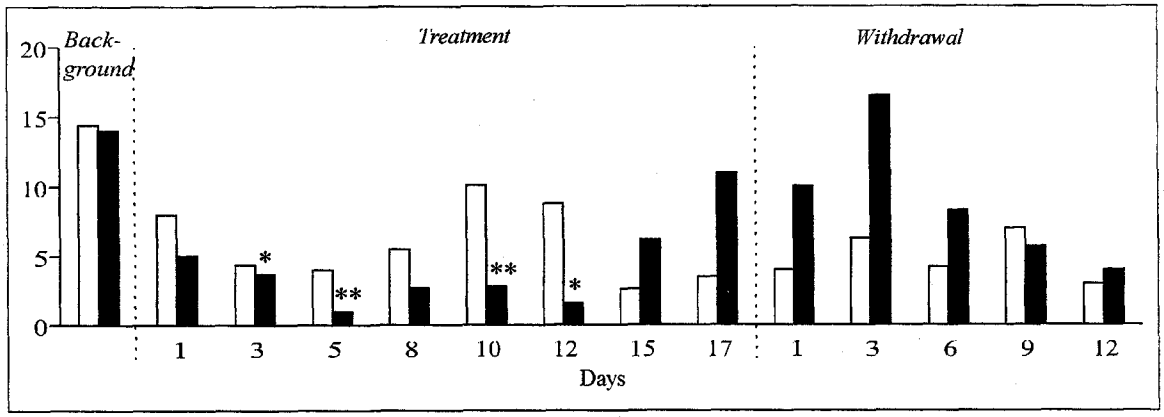

Fig. 1. Effect of repeated microinjections of 0.5 μl physiological saline (open bars) and 5 μg haloperidol (shaded bars) into globus pallidus on spontaneous motor activity. Ordinate: number of crossed squares during 5-min open field test. Here and in Fig. 2: p=0.01-0.05: *compared with baseline values, **compared with the corresponding control.

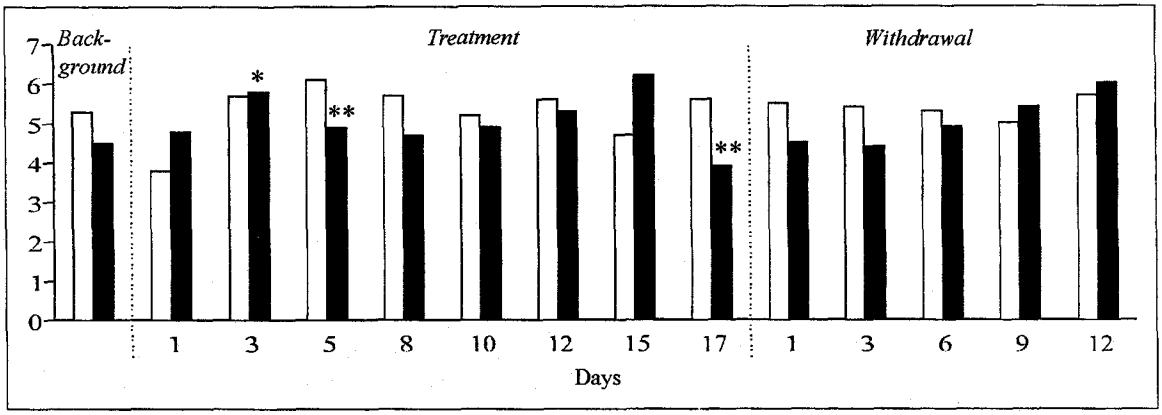

Fig. 2. Effect of repeated microinjections of 0.5 μl physiological saline (open bars) and 5 μg haloperidol (shaded bars) into globus pallidus on the latency of avoidance reaction. Ordinate: latency, sec.

of the pallidal dopaminergic system is accompanied by vegetative and trophic disturbances typical of experimental pallidotomy in animals [3] and parkinsonian syndrome in men [8]. These vegetative disorders developed more slowly than motor disturbances, but persisted for a longer time after cessation of haloperidol MI into GP.

GP is a target structure for neurosurgical correction of parkinsonism [1,2]. Compared with thalamotomy, pallidotomy more effectively controls both tremor and muscular rigidity [7]. However, the use of pallidotomy is restrained (apart from more difficult stereotactical approach) by poor understanding of its physiological functions [3]. Our experiments showed that vegetative and parkinsonian symptoms and motor disorders are due to insufficiency of pallidal and rostral dopaminergic systems, respectively, while CNS does not play a role in these disturbances.

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