Locomotor Disturbances in Rats Induced by Repeated Picrotoxin Microinjections to the Globus Pallidus and Caudal Neostriatum

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Repeated bilateral microinjections of picrotoxin in doses of 1 and 5 μg in the globus pallidus or caudal neostriatum induce seizures and impair conditioned motor reactions, but not myoclonic hyperkinesis typical of pharmacological block of the rostral neostriatal GABAergic system. Picrotoxin injected in a dose of 15 μg induces significant toxic effects.

Key Words: *striatum; globus pallidus; GABAergic system; picrotoxin; neuromotor dyskinesia; conditioned avoidance reaction*

Analysis of the activity of transmittory systems in various brain structures is important not only for understanding their regulatory role for physiological functions, but also for evaluating neurotransmittory pathogenetic mechanisms of neurological and psychopathological disturbances. In rat experiments, single [5] or repeated [3] microinjections (MI) of γ-animobutyric acid (GABA), a picrotoxin antagonist to the rostral neostriatum (NS), induced sustained extrapyramidal disturbances in the form of choreic myoclonic seizures of the limbs, head, and body. These data suggest that GABAergic system of the rostral NS is involved into the pathogenesis of hyperkineses. However, the role of GABAergic system in other basal ganglions remains unclear. In the present study we compare the effects of repeated injections of the GABA receptor blocker picrotoxin in the globus pallidus (GP) and caudal NS with our previous data on the role of the rostral NS in locomotor disturbances in rats.

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MATERIALS AND METHODS

Experiments were carried out on 38 male Wistar rats weighing 250-300 g. The animals were trained the active avoidance response in a shuttle box [3,4]. Polyethylene cannulas containing sterile apyrogenic physiological saline (control) or picrotoxin (Serva) were implanted bilaterally to GP and caudal NS under Hexenal narcosis. Stereotactic coordinates for GP were 0.8-1.0 mm caudal to the bregma, 1.8-2.8 lateral to the median scull line, and 7.0-7.5 mm ventral to skull surface, and the corresponding coordinates for caudal NS were 0.5-0.8, 1.0-1.5, and 6.0-6.5 mm, respectively. Procedure of MI was described previously [2,3]; the doses for each MI were 1, 5, and 15 μg. Each experimental group consisted of 4-6 animals. Experiments were started 2-3 days postoperation. The preparations were injected daily for 3 weeks. Behavioral tests were performed 3 times per week at 1-2-day intervals: 15-20 min after MI, 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 the experiments the rats were sacrificed under Hexenal narcosis and histomorpho-

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logical control was performed. Only the data obtained on animals with precise bilateral localization of the caudal NS and GP cannulas were taken into consideration and processed statistically using the Student *t* test.

RESULTS

Control rats had no locomotor disturbances. Active avoidance reaction was slightly impaired after the first few MI, but later this parameter did not differ from normal. Spontaneous motor activity and the latency of conditioned reaction remained unchanged.

Picrotoxin injected into GP in a dose of 15 μg induced pronounced neurotoxic effects. Muscular cramps, chaotic movements, jumping, and screaming were noted in the early postoperation period soon after awakening from narcosis (about 30-40 min after implantation of picrotoxin-containing cannulas). Two out of 5 rats died before the start of the treatment and others after the first few MI; their death was preceded (starting from the 5rd-7th min postinjection) by symptoms observed early postoperation, but more pronounced. Taking these and previous data [3] into account, we stopped MI of this dose of picrotoxin into the caudal NS.

Injection of 5 μg picrotoxin into GP did not induce postoperative motor disturbances; however, 4 out of 6 rats died during the first week of MI, while the survivors completely lost the conditioned skills. Injections of 1 μg picrotoxin into GP caused no death, had no toxic effect, and practically completely destroyed conditioned behavior in rats: correct responses did not exceed 40-50% over the experimental group and their latency was longer than in the control (Fig. 1). After termination of MI, these parameters slowly returned to normal.

Injection of 5 μg picrotoxin into the caudal NS induced myoclonic jerks of the head and body similar to those observed after MI of the same dose into the rostral NS [3,4]. However, hyperkineses were shorter in duration (from the 10th-15th to 60th-70th min postinjection) and were observed only during the first week of MI (injection of 5 μg picrotoxin into the rostral NS induced hyperkineses throughout the 3-week MI cycle). There were also qualitative differences, in particular, the hyperkinesis generalization stage was absent. Psychomotor agitation and enhanced spontaneous motor activity in this group were noted only after the first MI of 5 μg picrotoxin, but conditioned behavior was impaired in both the beginning and end of the MI cycle (Fig. 2).

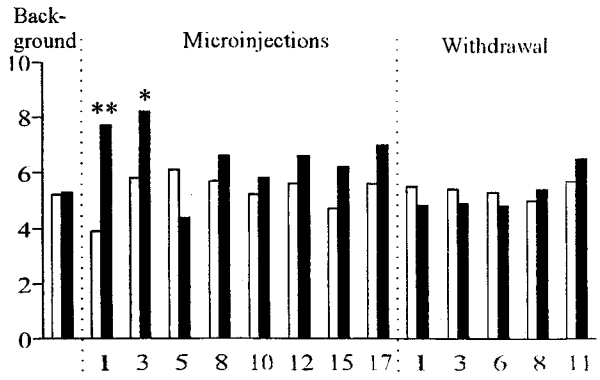

Fig. 1. Effect of repeated bilateral injections of 0.5 μl physiological saline (open bars) and 1 μg picrotoxin (shaded bars) into globus pallidus on the latency of conditioned avoidance reaction. Ordinate: latency, sec. Here and in Fig. 2: abscissa: day of testing. *p=0.05, **p<0.01 compared with the control.

Injections of 1 mg picrotoxin into the caudal NS induced neither motor disturbances nor significant impairment of conditioned behavior (Fig. 2).

Our findings suggest that choreic myoclonic high-amplitude (coarse) hyperkinesis of the body and limbs (similar to that in Huntington's chorea and chorea minor in rheumatic attack in men) can be induced by blockade of the GABAergic system in the rostral NS, but not GP; in a smoothened form it was observed after injection of picrotoxin into the caudal NS. Picrotoxin injected into GP

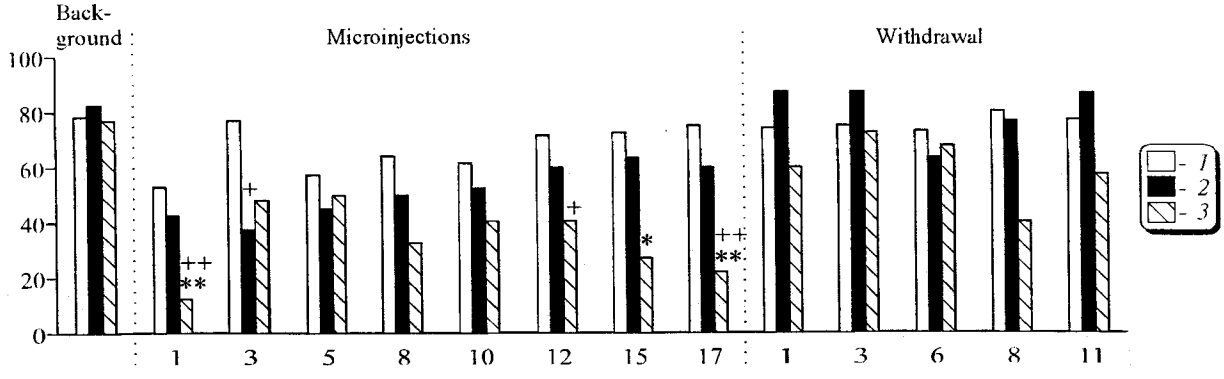

Fig. 2. Effect of repeated bilateral injections of 0.5 μl physiological saline (*1*), 1 μg (2), and 5 μg (3) picrotoxin into caudal neostriatum on the conditioned avoidance reaction in shuttle box. Ordinate: number of realizations, % of presentations. *p=0.05, **p<0.001 compared with the control.

induced seizures probably due to disturbed functional relationships between its two segments [5]. Being injected to the three basal structures, picrotoxin similarly inhibited conditioned behavior in rats. These findings demonstrate primary antihyperkinetic role of the rostral NS in rats, the analog of the caudate nucleus in primates and subprimates [1]. Thus, a characteristic feature of the blockage of the rostral and, to a lesser extent, caudal NS is the transmittory shift, i.e., predominance of dopaminergic influences of the substantia nigra, while inhibition of these influences is known to prevent hyperkineses [4]. The delicate striatal transmittory interactions involved into pathogenesis of hyperkinesis call more comprehensive investigations.

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