Activation of Neostriatal Dopaminergic System in Rats Prevents Toxic Effects of Picrotoxin Administered into Globus Pallidus

A. F. Yakimovskii

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Multiple bilateral microinjections of 5μg picrotoxin (antagonist of chloride channels coupled with $GABA_A$ receptors) into the globus pallidus induced lethal seizures in some rats and impaired conditioned avoidance responses in survivors. Administration of 15 μg amphetamine into the rostral neostriatum prevented picrotoxin-induced lethal seizures and reduced its negative effects on active avoidance behavior. Activation of the neostriatal dopaminergic system in animals receiving no intrapallidal picrotoxin promoted recovery of conditioned responses after implantation procedure.

Key Words: *neostriatum; globus pallidus; GABA- and dopaminergic systems; picrotoxin; amphetamine; active avoidance*

Subcortical nuclei of the extrapyramidal motor system (neostriatum and paleostriatum) play an important role in the pathogenesis of various motor disorders. Chronic experiments on rats with multiple picrotoxin microinjections into the globus pallidus (GP) showed that the paleostriatal GABA-ergic system is involved in choreomyoclonic hyperkineses [3]. The inhibitory effects of the neostriatum on nigral and pallidal structures are mediated by GABA [1,5]. There is evidence that both the development and severity of paleostriatal dystonia [4] and seizures (including convulsions induced by the blockade of the GABAergic pallidal system) depend on functional activity of the neustriatum.

In this study we investigated the effects of activation of the neostriatal dopaminergic system on motor abnormalities induced by intrapallidal microinjections of picrotoxin.

MATERIALS AND METHODS

The study was carried out on 24 male Wistar rats (200-250 g) preliminary trained an active avoidance task in a shuttle box. Polyethylene cannulas filled with sterile apyrogenic saline, amphetamine, and picrotoxin (Sigma) were stereotactically implanted in the rostral neostriatum (RN) and GP under hexenal anesthesia (75-100 mg/kg). Implantation coordinates for RN were 1.0-1.5 rostral to bregma, 2.0-2.5 mm lateral to midline, 6.0-6.5 mm below the surface of the skull and the coordinates for GP were 0.8-1.0 mm, 1.8-2.8 mm, and 7.0-7.5 mm, respectively. Microinjections into RN (0.75 μl) and GP (0.5 μl) were performed as described earlier [2]. Single doses of amphetamine and picrotoxin were 15 and 5 μg, respectively. The rats of the control group received saline into RN and GP. Group 1 received intrastriatal amphetamine and intrapallidal saline, group 2 — intrastriatal saline and intrapallidal picrotoxin, group 3 — intrastriatal amphetamine and intrapallidal picrotoxin. Each group consisted of 5-7 animals. The experiments started 2-3 days after implantation. The drugs were injected daily into both structures simultaneously for 3 weeks. Behavioral tests were performed 3 times a week with 1-2-day intervals: 15-20 min after microinjections spontaneous activity in an open field was recorded and then active avoidance behavior was evaluated for 5 min. Behavioral tests were continued for 2-3 weeks after cessation of microinjections, then the animals were sacrificed for histomorphological verification.

Department of Normal Physiology, I. P. Pavlov State Medical Academy; Laboratory of Physiology of the Higher Nervous Activity, I. P. Pavlov Institute of Physiology, St. Petersburg. ***Address for correspondence:*** martyn@spmu.rssi.ru. Yakimovskii A. F.

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The data collected from animals with accurate bilateral injections into RN and GP were analyzed statistically using Student's *t* test.

RESULTS

Abnormal motor activity in control rats and group 1 animals manifested in impaired active avoidance performance. This effect was more pronounced in the control group, especially on days 1-5 of microinjections (Fig. 1, *1, 2*). These findings agree with previous observations [3] and can be attributed to surgical trauma. Activation of the neostriatal dopaminergic system partially reversed these negative effects of implantation procedure. Controls and group 1 rats showed no significant changes in the latency of conditioned avoidance. In group 1 rats spontaneous activity significantly (7-8-fold) surpassed the initial level after days 12-13 of microinjections. Hyperactivity with elements of exploratory stereotypes (sniffing) persisted after cessation of microinjections.

In group 2 animals, motor abnormalities such as skeletal muscle seizures (appeared 4-6 min postinjection) were observed against the background of disorganized ambulations and jumps. Four of 7 rats died during the first week of treatment, while in survivors conditioned responses were absent (Fig. 1, *3*) during treatment and only partially recovered after termination of treatment (the mean number of correct responses did not exceed 20-25%). The latency of conditioned avoidance exceeded the control value. Intrastriatal injections of amphetamine completely prevented neurotoxic effects of picrotoxin: group 3 rats showed no convulsions or impulsive movements and no lethal seizures. Avoidance behavior was impaired compared to the control, but exceeded that in group 2 (Fig. 1, *4*). The latency of avoidance responses varied considerably. Spontaneous activity in the open field test increased only on days 1 and 3 of microinjections; exploratory stereotypies were absent.

These data show that activation of the neostriatal dopaminergic system significantly affects motor behavior. Intrastriatal injections of amphetamine abolished the negative effects of surgery and bilateral intracerebral (RN and GP) injections of saline on active avoidance behavior. Activation of the neostriatal dopaminergic system prevented convulsions and lethal seizures caused by inactivation of the pallidal GABAergic system with picrotoxin. These phenomena can be explained by direct effects of amphetamine on striopallidal interactions blocking the effects of picrotoxin. However, they can also be due to more complex rearrangements of the intrastriatal relationships. For instance, intrapallidal picrotoxin can affect GABAergic pathways from GP to the neostriatum [5]. Inactivation of this GABAergic pathways can be compensated by activation of the neostriatal dopaminergic system. It is noteworthy that the blockade of pallidal $GABA_A$ receptors reduced the efficiency of intrastriatal amphetamine: under these conditions amphetamine did not induced stereotypes. Our findings and published data suggest close and complex interrelations between the neo- and paleostriatum, which are largely mediated by dopamine- and GABA-ergic systems. Coordinated activity of the neostriatum and GP is an important factor of resistance to motor dysfunction.

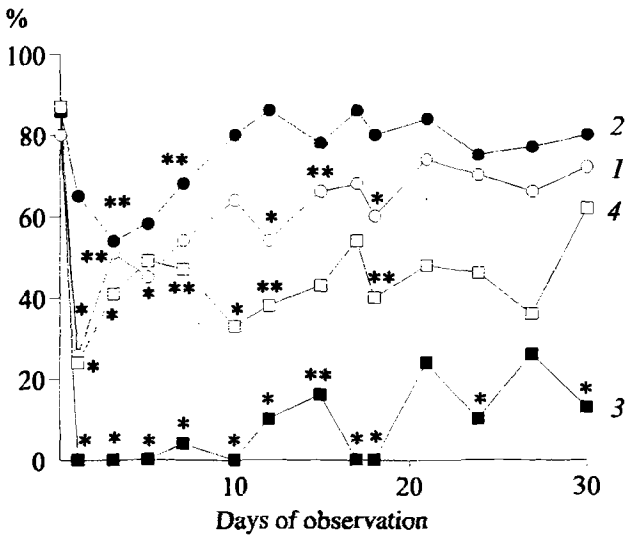

Fig. 1. Effect of multiple injections of amphetamine (15 μg) and picrotoxin (5 μg) into the rostral neostriatum (RN) and globus pallidus (GP). *1*) control (saline into RN and GP); *2*) amphetamine into RN, saline into GP; *3*) saline into RN, picrotoxin into GP; *4*) amphetamine into RN, picrotoxin into GP. Ordinate: number of avoidance reactions (% of trials). 1-17 days: daily microinjections; 18-30 days: after cessation of microinjections. $^*p<0.01$, $^{**}p<0.05$ in comparison with the control.

REFERENCES

1. V. A. Otellin and E. B. Arushanyan. *Nigrostriatal System* [in Russian], Moscow (1989).
2. A. F. Yakimovskii, *Ros. Fiziol. Zh.*, **84**, No. 6, 906-912 (1998).
3. A. F. Yakimovskii, *Byull. Eksp. Biol. Med.*, **126**, No. 10, 381-383 (1998).
4. A. Berardeli, J. C. Rothwell, M. Hallet, *et al.*, *Brain*, **121**, No. 7, 1195-1212 (1998).
5. H. J. Waldvogel, J.-M. Fritschy, H. Mohler, *et al.*, *J. Comp. Neurol.*, **397**, No. 3, 297-325 (1998).