A loss of short-latency excitatory caudate unitary responses to motor cortex but not to motor thalamic nuclei stimulation in MPTP-treated cats

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Abstract. The effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP, 5 mg/kg i.m. for 5 days) on the evoked activity of caudate neurones were studied extracellularly in ketamine-anaesthetized and myorelaxant-immobilized cats. Two days after the last MPTP injection the latency of caudate neurone responses to the motor cortex stimulation increased as compared to intact animals, due to a 10-fold decrease in the number of neurones with short-latency responses (from 1.8 up to 8.0 ms). At the same time, no essential changes were observed under the influence of MPTP in the distribution pattern of the latency of caudate neurone responses to the stimulation of the ventral anterior and ventral lateral nuclei of the thalamus. The suggestion that dopamine protects monosynaptic transmission of impulses from the cerebral cortex to neostriatum neurones is discussed.

Key words: caudate neurones, neuronal evoked activity, motor cortex, MPTP, cat
The morphological and electrophysiological studies have shown the presence of three principal sources of afferent projections to nerve cells of mammalian neostriatum: (1) glutamatergic neurones of the cerebral cortex, especially of its frontal areas; (2) neurones of the thalamic nuclei including motor ones - ventral anterior (VA) and ventral lateral (VL), the nature of their neuroactive substances being at present still unknown; (3) dopaminergic neurones of the compact part of the substantia nigra. According to morphological data, the terminals of these afferents form synapses mainly with dendritic spines of the neostriatal nerve cells. Axoaxonal synapses are occasionally encountered (see reviews Feger 1981, Groves 1983, Kornhuber and Kornhuber 1986). However, the results of autoradiographic studies suggest that a great number of dopaminergic receptors are localized on the terminals of cortical afferents, but not on thalamic afferents (Schwarcz et al. 1978, Robert-son 1986).

In the present work the existence and functional meaning of axoaxonal dopaminergic synapses on cortical afferents of cat caudate nucleus have been investigated with the use of MPTP. The neurotoxin MPTP is known to exert a selective damage of dopaminergic neurones of the nigrostriatal system of mammals (Sanchez-Ramos et al. 1986, Ambrosio et al. 1987, Schwartzman et al. 1988) including cats (Schneider et al. 1986, Voloshin et al. 1989, Williams and Schneider 1989), and to provoke symptoms very similar to those of human parkinsonism (Schneider et al. 1986, Schwartzman et al. 1988, Williams and Schneider 1989). The effects of MPTP on caudate neurone responses evoked by stimulation of the motor cortex MI and VA and VL thalamic motor nuclei have been compared.

The studies were conducted on two groups of cats (males) weighing 3.0-6.0 kg. Nineteen animals of the first group served as a controls (intact). Aqueous solution of MPTP (1%) was administered i.p. to 14 animals of the second group for 5 days at a dose of 5 mg/kg daily. Two days following MPTP treatment, the dopamine level decreased by about 70% in cat neostriatum (Voloshin et al. 1989). The procedure of acute experiment performed two days after the termination of neurotoxin injections was identical in the experimental and control group of animals. Tracheotomy, catheterization of femoral vein, and preparative cranial operations were done under ketamine anaesthesia (25 mg/kg i.m.), with additional local anaesthesia of soft tissues in the region of the operative field using 0.5% solution of novocain. The animals were immobilized with myorelaxin and artificially ventilated. To maintain optimal functioning of the body, we used a controlled breathing, and continuous intravenous infusion of 3.5 ml polyglucin + 0.1 ml 40% glucose + 0.02 ml cordiamin per kg per hour. The temperature of the animal body was kept at 37°C. Single unit activity of caudate neurones was recorded extracellularly at the level of frontal planes A-18.5 - A-15.0 (Jasper and Ajmone-Marsan 1954) by glass microelectrodes filled with 2 M potassium acetate having DC resistance of 5-10 MΩ.

To stimulate cortical fields 4 and 6, eight stainless steel needle electrodes (the interelectrode distance - 0.5

![Fig. 1. The example of orthodromic responses of a caudate neurone evoked from the cortex. Caudate cell was activated by stimulation (arrows) of the pericruciate (motor) cortex and had response latencies of 2.0 ms (1). Spontaneous discharges (S) were used to collide spikes by triggering the oscilloscope trace and delayed stimulus pulses (arrows) 330 μs (2), 400 μs (3), and 540 μs (4). Note a negative collision test in (4). Five to seven superimposed oscilloscope tracings of the neuronal response. All stimuli are presented at 1.5 x the threshold. Calibration bars: 2 ms, 1 mV.](image)
mm) were submerged into the cortex at a depth of 2.0 mm. To stimulate the VA-VL region at the level of frontal planes A-12.0 - A-10.0 (Jasper and Ajmone-Marsan 1954), four electrodes 0.12 mm in diameter (the interelectrode distance - 0.1 mm) insulated at the whole length except for the tip were used. Single monophasic square pulses up to 150 μA, duration - 0.2 ms and with the frequency not exceeding 0.5 s-1 were used for stimulation. At least 20 successive responses displayed on an oscilloscope were photographed. Postsynaptic spikes were identified as those that failed to satisfy the criteria for antidromic spikes (Fig. 1). Criteria for antidromic activation were a fixed latency, the ability to follow fast stimulation rates, and collision with spontaneous or synaptically evoked spikes (Lipski 1981).

After the experiment the cats were sacrificed by thiopental i.v. injection. The recording and stimulating sites were marked by passing a direct current of 20 μA for 20 s. The location of recorded neurones was reconstructed on the histological section from lesion sites and micrometer reading.

The excitatory responses in the form of one or several action potentials were recorded in the dorso-lateral part of the head and body of caudate nucleus from 67 neurones in 10 control experiments and from 84...
neurones in 8 MPTP-treated animals in response to the cortex stimulation. In control animals, the neurones responding to cortical stimulation practically the same ratio between spontaneously active and silent neurones of the caudate nucleus (34 and 33, respectively). After MPTP treatments the number of spontaneously active neurones was reduced 5 times as compared with that of silent neurones (14 and 70, respectively). The latency of responses varied from 1.8 up to 35.0 ms (on the average 14.7 ± 1.0 ms) in the control and from 4.5 up to 30.5 ms (on the average 18.2 ± 0.7 ms) in the neurotoxin - treated animals. A significant increase in the discharge latencies duration as compared with that in the control animals (P < 0.05, nonparametric Mann-Whitney U-test) occurs due to a 10-fold decrease in the number of neurones with the short-latency responses from 1.8 up to 8.0 ms: 23.9% and 2.4% of all caudate neurones in the control and MPTP-treated animals, respectively (Fig. 2).

According to Kocsis et al. (1977), the latency of monosynaptic excitatory postsynaptic potential EPSP arising in caudate neurones in response to cortical stimulation in cats reached 12.0 ms. So, an increase in the latency of the responses of caudate neurones to the cortex stimulation of MPTP-treated animals should occur, probably, due to a blockade of impulses passing along the monosynaptic cortico-neostriatal pathways.

The excitatory responses were also recorded in the form of one or several action potentials in the lateral and medial parts of the head and body of caudate nucleus in response to the stimulation of the VA-VL region. In nine animals of the control group 67 neurones, and 80 neurones in 6 MPTP-treated animals were investigated. In control animals, the neurones responding to thalamic stimulation showed practically the same ratio between spontaneously active and silent neurones of the caudate nucleus (31 and 32, respectively; we failed to determine the state of spontaneous activity in 4 cells). After MPTP injections the number of spontaneous active neurones was reduced 2.3 times as compared with that of silent neurones (22 and 50, respectively; we failed to determine the state of spontaneous activity in 8 cells). The latency of responses varied from 1.8 up to 28.7 ms (on the average 10.1 ± 0.7 ms) and from 1.9 up to 26.5 ms (on the average 10.1 ± 0.7 ms) in the control and MPTP-treated animals, respectively. The histograms presented in Fig. 3 show that no essential changes are observed in the distribution pattern of the latency of responses of caudate neurones to the thalamic stimulation.

The ambiguous effect of MPTP on the impulse transmission to caudate neurones from the cortex and thalamus evidences the presence of dopaminergic synapses on the corticoneostriatal terminals. One may consider that dopamine release in these synapses exerts a protective effect on the monosynaptic transmission of impulses from the cerebral cortex to neostriatal neurones. The point is that MPTP-induced deficiency of dopamine may create conditions for insufficient inhibition of corticofugal impulsion and excessive release of glutamate. In these cases glutamate exerts a toxic action (Olney et al. 1986, Lysko et al. 1989) on neostriatal neurones or on their glutamate receptors. This supposition is also confirmed by the disappearance of the short-latency responses of the neostriatal neurones to stimulation of the sensorimotor cortex in rats depleted of endogenous dopamine by treatment with reserpine (Johnson et al. 1983). Besides, a substantial increase in the number of neostriatal silent neurones responding either to cortical or thalamic nuclei stimulation discovered under MPTP action can be accounted for by a reduction of excitatory afferentation of the neostriatum due to a blockade of multiple corticoneostriatal glutamatergic inputs.

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