# ROLE OF CATECHOLAMINERGIC MECHANISMS AND THE CAUDATE NUCLEUS IN THE DEVELOPMENT OF GENERALIZED CONVULSIONS CAUSED BY PARENTERAL INJECTION OF PENICILLIN

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The behavioral and EEG changes induced by a single intramuscular injection of large doses of penicillin were recorded in unrestrained cats. The eyes closed tightly and myoclonic spasms appeared, accompanied by slow negative waves and spike-wave complexes in the cortex and caudate nucleus. Stimulators of catecholaminergic transmission (L-dopa and apomorphine) interfered with the development of these phenomena but facilitated the triggering of tonicoclonic convulsions. Inhibitors of catecholaminergic transmission (chlorpromazine and haloperidol) had the opposite effect. Electrolytic injury to the head of the caudate nucleus also interfered with the formation of phenomena similar to a minor epileptic fit, whereas threshold low-frequency stimulation of the nucleus, on the other hand, potentiated the effect of penicillin.

KEY WORDS: penicillin convulsions; catecholaminergic drugs; caudate nucleus.

As the writers showed previously, the behavioral and electroencephalographic manifestations of the preconvulsive action of metrazole in rats, resembling the picture of a minor epileptic fit, were reduced in intensity following administration of stimulators of central catechloaminergic transmission and were potentiated by its inhibitors. Precisely the same opposite effects on the dynamics of the preconvulsive state were produced by blocking and stimulation of the corpus striatum [1-5].

Prince and Farrell [7] described a model of generalized epilepsy in cats produced by intramuscular injection of large doses of penecillin. In the opinion of Gloor and Testa [6, 9], penicillin convulsions of this type resemble most of all the myoclonic form of petit mal in man. With these facts in mind, it was interesting to study the effect of changes in catecholaminergic transmission and in the activity of the caudate nucleus, the leading component of the corpus striatum which is dependent on it, on penicillin convulsions.

## EXPERIMENTAL METHOD

Experiments were carried out on 58 adult cats of both sexes weighing 1.8-3.5 kg, divided into three groups. Group 1 (24 cats) consisted of intact animals. Group 2 (22 cats) consisted of animals in which the EEG was recorded and the caudate nucleus stimulated. For this purpose, steel needle electrodes to record the ECoG were inserted into different parts of the neocortex under pentobarbital anesthesia, and activity of the caudate nucleus was derived by a monopolar nichrome electrode inserted into its head (level A18-A17 according to the stereotaxic atlas [8]. Meanwhile bipolar nichrome electrodes (0.2 mm, interpolar distance 0.5 mm), through which the brain could be stimulated (frequency 1-10/sec, duration 0.5 msec), were implanted into the head of the opposite nucleus of the same animal. In some cats the nucleus was stimulated without recording the EEG. Group 3 (12 cats) consisted of animals with bilateral destruction of the head of the caudate nucleus (silver electrodes, direct current, 2 mA, 90 sec).

To induce convulsions in cats of all groups, the sodium salt of benzylpenicillin (400,000-500,000 units/kg) was injected once, intramuscularly. The latent period of the

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TABLE 1. Effect of Catecholaminergic Drugs Administered against the Background of Formed Penicillin Convulsions on the Number (N) and Duration (D) of Bursts of SNW in the Cat Sensomotor Cortex

| Penicillin + stimulators of catecholaminergic transmission | | | | | | | Penicillin + inhibitors of catecholaminergic transmission | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cat No. | control | | L-dopa 100 mg/kg | | apomorphine 5 mg/kg | | Cat No. | control | | chlorpromazine 5 mg/kg | | haloperidol 1 mg/kg | |
| | N | D | N | D | N | D | | N | D | N | D | N | D |
| 2 | 30 | 2,2 | 4 | 0,4 | 10 | 0,8 | 19 | 18 | 1,8 | 30 | 3,2 | 28 | 3,2 |
| 10 | 28 | 1,8 | 5 | 0,3 | 8 | 0,6 | 20 | 14 | 1,6 | 38 | 2,8 | 32 | 3,0 |
| 15 | 32 | 2,4 | 4 | 0,5 | 12 | 0,9 | 22 | 8 | 1,3 | 44 | 2,6 | 24 | 2,9 |
| 21 | 38 | 2,0 | 6 | 0,3 | 14 | 0,8 | 38 | 16 | 1,4 | 48 | 2,9 | 28 | 3,5 |
| 42 | 20 | 2,1 | 3 | 0,7 | 18 | 1,1 | 42 | 20 | 2,1 | 22 | 2,2 | 20 | 2,4 |
| 45 | 24 | 1,9 | 1 | 0,6 | 8 | 0,5 | 43 | 12 | 1,5 | 55 | 2,2 | 19 | 3,1 |
| | 28,7±2,8 | 2,01±0,12 | 2,1±1,3 | 0,47±0,13 | 10±2,8 | 0,68±1,8 | | 14,7±2,1 | 1,61±0,21 | 39,5±5,7 | 2,71±0,26 | 25±2,5 | 3,01±0,25 |

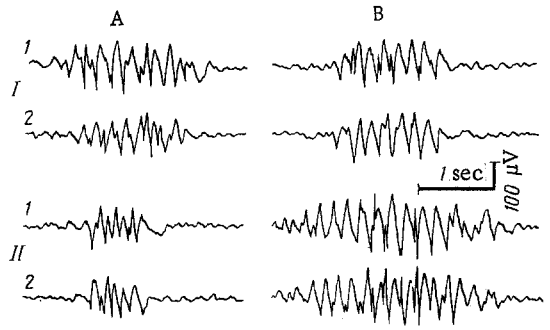


Fig. 1

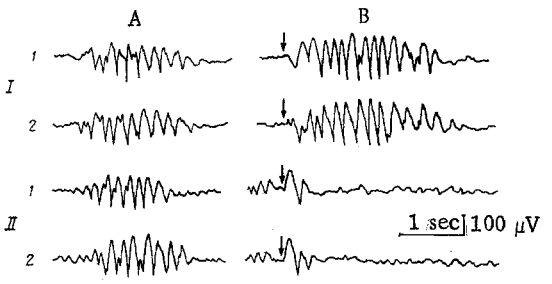


Fig. 2

Fig. 1. Effect of L-dopa and haloperidol on penicillin paroxysmal discharges. A) Control; B) after preliminary administration of drugs. I) 15 min after L-dopa (50 mg/kg), II) 15 min after haloperidol (1 mg/kg). 1) Sensomotor cortex; 2) caudate nucleus.

Fig. 2. Effect of caudate stimuli of varied intensity on SNW and spike-wave complexes provoked in cats by penicillin. A) Before, B) during application (arrow) of caudate stimulus. Head of caudate nucleus stimulated by current of 14 V (I) and 30 V (II). 1) Sensomotor cortex; 2) caudate nucleus.

convulsions was measured until the appearance of the first myoclonic spasm (MCS), and their frequency (in 5 min) was determined 30, 60, 90, and 120 min after the injection; the character of the convulsion was noted.

The pharmacological agents were injected intraperitoneally in the following doses: L-dopa 20, 50, and 100 mg/kg; apomorphine 1 and 5 mg/kg; chlorpromazine 3 and 5 mg/kg; haloperidol 1-3 mg/kg. They were used in accordance with two schemes. In half of the animals of groups 1 and 2 the characteristics of the penicillin convulsions were assessed initially, and 2 to 3 days later the action of the antibiotics was studied 20-30 min after injection of one of the drugs. The other half of the animals, after the first control determination of the effect of penicillin, received the drugs after the formation of definite penicillin MCS. The experiments lasted 3 months with an interval of 2-3 days. After they had ended, a series of frontal sections of the brain was cut for determining the location of the stimulating and recording electrodes in accordance with the coordinates of the atlas. The volume of brain damage was calculated in the animals with destruction of the caudate nuclei.

## EXPERIMENTAL RESULTS

Characteristic tight closing of the eye appeared 15-20 min after injection of penicillin into the animals. Meanwhile high-amplitude slow negative waves (SMW) were recorded in different derivations of the EEG. After a further 10-20 min the pattern of a minor epileptic fit developed: All movements ceased, convulsive spasms of the muscles of facial expression, tremor of the head, and MSC of varied intensity were observed. In all derivations of the ECoG hypersynochronous SMW and spike-wave complexes with a frequency of 3-4 waves/sec was observed. They appeared sooner and were more marked in the occipital cortex and caudate nucleus. The epileptiform phenomena reached their maximum, with well-marked and frequent MCS, after 60-90 min. If L-dopa and apomorphine were injected against the background of well-developed penicillin convulsions, they had an inhibitory action. The number of MCS fell sharply 10-15 min after injection of the drugs. The changes in paroxysmal activity were particularly clear on the EEG. The number of bursts of SMW and spike-wave complexes was reduced and their duration was shorter. On the whole apomorphine caused less marked changes than L-dopa (Table 1). In some animals (15%), after a short series of well-developed MCS against the background of penicillin a psychomotor and also a generalized tonicoclonic fit developed immediately.

If the drugs were administered in the opposite combinations — penicillin was given after L-dopa or apomorphine — similar results were observed. A significant lengthening of the latent period of the convulsions was observed first of all. In the case of L-dopa, for example, it was 142±16.2 min, compared with 33.8±3.5 min in the control. The number of MSC also was reduced by 67-80% compared with their number at the height of the convulsions. However, the marked increase in intensity of MSC must be noted. According to the EEG data, penicillin

after L-dopa and apomorphine caused shorter bursts of SNW and spin-wave complexes. The morphology of the epileptiform discharges also was changed: sharp waves and spikes predominated over SNW (Fig. 1).

The neuroleptics chlorpromazine and haloperidol had the opposite action. Against the background of as yet unformed paroxysmal phenomena, they sharply potentiated the action of penicillin. The fit developed more rapidly and MSC were appreciably more frequent. The number of MSC increased under the influence of chlorpromazine 20-30 min after injection of the antibiotics, from 8-10 to 30-55 in 5 min, for example. At the height of the convulsions the effect was less clear but in the same direction. Bursts of SNW and of spike-wave complexes were more frequent on the EEG and longer in duration (Fig. 1). On the whole, chlorpromazine increased the number of MSC and SNW more sharply than haloperidol.

When the neuroleptics were given before penicillin the dynamics of the convulsions, on overall assessment, showed little change. The mean latent periods and frequencies of MSC were close to the control levels, although changes in individual cases were sufficiently clear. This was because the substances acted in different directions in individual animals.

The formation of myoclonic spasms and their EEG accompaniment was impaired 7-8 days after partial (20-35% of the volume) bilateral caudatectomy. This was shown by a considerable lengthening of the latent period of MSC and an increase in their number (on average from 35.8±5.7 to 50.2±10.7). The character of the convulsions changed at the same time. Often (30% of cases) psychomotor excitation developed at the height of the action of penicillin, with frequent turnings of the head from side to side, and even running in a circle. This excitation regularly ended with generalized tonicoclonic convulsions in two cats (Nos. 15 and 36). Desynchronization of activity of the different cortical zones was typical of the EEG of the caudatectomized animals. As the effect of penicillin increased, paroxysmal discharges began to be formed far earlier than in the control. Features of the caudatectomized animals were polymorphism of activity and predominance of spike-wave complexes on the EEG. The number of bursts of SNW also fell sharply — to 8-10 in 5 min (from 32-34 in the control).

Against the background of brain damage, potentiation of the anticonvulsive properties of L-dopa was observed. If it was injected at the height of a minor fit, MSC in general were no longer formed, but by contrast cases of formation of psychomotor excitation were more frequent, with subsequent transition into a tonicoclonic fit, which terminated in three cats (Nos. 36, 41, and 49) by status epileptiformis. Haloperidol, on the other hand, increased the frequency of MSC, although their total number remained less in all the experimental animals than in the controls (10-12).

Infrequent (1-3/sec) caudate stimuli of below threshold strength for behavioral manifestations, or producing extremely weak twitches of the head in rhythm with brain stimulation, could trigger penicillin convulsions. An essential condition for this was the presence of at least the first epileptiform discharges, and application of the electric shock in the interparoxysmal period (3-5 sec after the end of a "spontaneous" burst). In such a situation, brain stimulation provoked marked MSC. Epileptiform reactions were generated much more frequently on the EEG, they were longer than "spontaneous" discharges, and they acquired the features of spike-wave discharges sooner (Fig. 2). Caudate effects were greatly weakened against the background of L-dopa, but neuroleptics, on the other hand, definitely prolonged the responses caused by stimulation of the nucleus.

Functional (by means of L-dopa or apomorphine) and morphological inactivation of the nucleus thus weakens the manifestations of penicillin convulsion that closely resembles the picture of a minor epileptic fit. On the other hand, neuroleptics which mobilize the nucleus, or its electrical stimulation, have an anticonvulsant effect. On the whole this agrees with the writers' earlier observations on rats with metrazole convulsions [1-4] and, despite certain differences, it underlines the single neurochemical and neurophysiological organization of the two models of convulsions. The possibility of controlling the paroxysmal process through selective interference with the activity of the dopaminergic (nigrostriatal) brain mechanisms, would appear to be important and of practical value for the treatment of minor fits.

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# RECOVERY OF MOTOR FUNCTIONS AFTER DIVISION OF THE SPINAL CORD OR CAUDA EQUINA

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Partial recovery of motor functions in 8 patients with division of the spinal cord at the mid-thoracic level or of the cauda equina at the lumbar level is described. During attempts by all patients at voluntary movement, electromyography revealed the development of activity in the trunk muscles and m. gluteus medius, as well as the appearance and development of activity in muscles of the thigh and leg. The level of rehabilitation in the patients was relatively high: They could walk with suitable support, they could work at their own trades, and they could care for themselves. Recovery of motor functions took place more rapidly after trauma at lower levels, although complete rehabilitation was achieved in two patients with trauma at a higher level. The mechanism of restoration of functions is based on the compensatory development of activity in the trunk muscles and the ability of the distal segment of the spinal cord to form new motor reflexes with the participation of the limb muscles.

KEY WORDS: recovery of motor functions; electromyogram; distal segment of the spinal cord.

The study of reflex activity of the spinal cord after division in dogs has shown that it differs considerably from normal [1]. The spinal cord "returns," as it were, to phylogenetically older forms, so that atypical motor responses can be formed in the animals. In dogs receiving extra afferent stimulation partial recovery of the motor functions of the hind limbs was observed.

In patients with complete transection of the spinal cord at the level of the thoracic vertebrae or at the lumbar level (cauda equina) remedial gymnastics and pyrogenal therapy can also lead to partial recovery of motor functions. Eight such cases are described below.

## EXPERIMENTAL METHOD

In six patients the diagnosis was established at laminectomy and it was confirmed in all eight patients by the results of neurological and electromyographic investigation [2]. The patients have been trained for different lengths of time by Doctor A. N. Trankvillitati.* Besides physical therapy, pyrogenal therapy also was given [3, 4]. During training the limb volume was investigated and the electromyogram (EMG) of the trunk and lower limb muscles was recorded during attempts at voluntary movement. The movements concerned were drawing up the lower limb by tilting the pelvis towards the shoulder, and also supporting the foot on a board placed by it. The EMG was recorded in the prone and supine positions. The method of

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