Tremor Induced by Iron Overloading

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In the past few years attempts have been made to reproduce extrapyramidal symptoms in experimental animals, especially the parkinsonian tremor. This has been achieved by administration of different chemical agents, or by causing minute injuries in the retrolignal mesencephalic tegmentum. Although these experiments do not necessarily relate to the factors causing paralysis agitans in man, valuable inferences have been obtained from their results.

The present work sprang from the finding of iron inclusions in thalamic neurons and glial cells of parkinsonian patients. The pathophysiological role of the intracellular iron has been explored by overloading experimental animals with iron-dextran (Imferon-Benger 1756/2).

Methods

The experiments were carried out in 12 monkeys (Cebus albifrons) and 100 rabbits. The animals received 100 mg iron-dextran per week, by intravenous injection. A thorough clinical examination was made every 14 days and sometimes filmed. Control animals were also used.

Electrographical (EMG) recordings were made through concentric stainless steel electrodes inserted in the muscles of neck and limbs without anesthesia. These recordings were made through capacity coupled preamplifiers. An EMG integral was obtained by means of a Grass integrator channel. The EMG activity was recorded on tape and later analyzed in a Computer Measurements counter timer.

Biochemical, cellular, and subcellular studies were also performed; these results will be reported later.

Results

Nine out of the 12 monkeys developed EMG abnormalities after receiving a cumulative dose of 500 mg iron-dextran; the rest of the monkeys died before the 5th week of injections because of intercurrent respiratory disease. Of the 100 rabbits, 71 showed the same kind of EMG abnormalities after 8 to 10 weeks of injections; 15 rabbits were sacrificed for biochemical and histological studies before a cumulative dose of 800 mg was attained; 14 rabbits died because of intercurrent disease, chiefly respiratory. In both species, clinical evidence of neurological disturbances was present from the 10th to the 14th week of treatment. In both species the clinical picture was characterized by motor disturbances and abnormal movement. The monkeys also showed poverty of emotional expression and loss of mimicry. The initial sign was increased tonus in the hind limbs.

In five rabbits, injections were stopped at the 20th week; no subsidence of clinical or EMG signs was evident after 10 weeks of further observations.

The animals tended to be immobile, moving clumsily; rabbits no longer hopped, but walked. Brisk, low-threshold deep reflexes were elicitable. There was strong flexor tone in all extremities. The resistance to passive extension was strongly increased in the hind limbs of rabbits.

Tremor was observed in the distal parts of the limbs, at rest or when the extremity was partially supported in a postural manner. The tremor was more evident in monkeys. It appeared as an alternating rhythmic flexion-extension movement at a frequency that ranged from 6 to 12 cycles/sec and was rather constant for each animal. The frequency most commonly observed was 8/sec.

In iron-overloaded animals, the EMG of the hind limb muscles showed the following characteristics:

1. A steady high rate of action potential,
also observed when the animal was apparently resting.

2. At a more or less constant periodicity the trace showed macropotentials, over a steady discharge of micropotentials (Fig. 1). Measurements of these intervals with the counter gave a range of 50 to 80 msec. The macropotentials evidently meant a synchronous discharge of motor units; palpation of these muscles revealed a fine tremor roughly corresponding to the frequency of these potentials.

3. When contraction of antagonists alternated, tremor of the corresponding segment appeared.

4. The area under the integral curve was two times smaller than the area obtained during muscular activity in normal animals (compare Fig. 2a' with Fig. 1b').

The EMG of the control animals showed the isoelectric resting conditions; muscular activity was only recorded after excitation of any kind. During muscular activity no tendency to periodic discharge of macropotentials was observed; the integral showed irregular, smooth variation (Fig. 2). The resting EMG trace of the limbs contrasted with steady muscular activity recorded at the neck. On the contrary, the iron-overloaded animals showed steady activity of both limbs and neck muscles.

Discussion

The iron-overloaded animals showed some motor disturbances, the most important of which was the periodic synchronous activity of the muscle fibers of limb muscles shown in the EMG. This qualitative change in the pattern of activity of the muscle fibers could only be mediated by the central nervous system (CNS). Therefore, the periodic pattern of muscular activity must be produced by the alpha motoneurons. This alteration is similar to that underlying tremor in man. If only quantitative changes had been observed, such as diminution of muscle strength, further proof of CNS involvement would have been required.

Histochemical and ultrastructure studies, which are still under way (G. Rojas, un-
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FIG. 2. a and b. Normal EMG of extensor and flexor crural muscles, Cebus albifrons. a'. Integral curve of a.

published data), so far show iron inclusions in neurons and glial cells of the cortex and basal ganglia of these animals. This means that the unbalanced activity of alpha motoneurons depends on influences descending from the encephalic level to the spinal cord. This also allows us to conclude that the motor disorders in these animals are structurally specified, i.e., they do not depend on pure functional disturbances.

The motor disturbances developed by these animals are analogous to those observed in paralysis agitans. Since iron inclusions in nervous tissue have also been observed in parkinsonian patients, the coincidence suggests that this structural alteration of the CNS may be an important factor in the motor abnormalities of paralysis agitans.

Summary

Twelve monkeys and 100 rabbits were injected weekly with 100 mg iron-dextran, with total doses of up to 4 to 5 gm. These animals developed signs similar to those observed in paralysis agitans, especially synchronous periodic activity of alpha motoneurons. Histopathological examinations showed iron inclusions in cortical and subcortical neurons and glial cells. These experimental observations in primates and rodents and similar observations in humans suggest that the alterations found in cortical and subcortical cells may determine the motor disturbances of paralysis agitans.

References