REVERSIBILITY OF CHANGES IN THE RAT BRAIN DUE TO PROLONGED ADMINISTRATION OF LYSERGIDE (LSD)

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The first signs of reversibility of the pathological changes in the rat brain after administration of lysergide for 4 weeks appeared 2 weeks after the end of its administration. A considerable proportion of the changes was reversible. At the same time, the existence of foci of rarefaction in cortical layers III-V must be interpreted as residual manifestations of brain damage caused by prolonged lysergide poisoning.

A single administration of even extremely small doses of lysergic acid and its derivatives (1-2 μg/kg) to man induces well-marked psychotic conditions resembling exogenic psychosis [7, 9, 10, 11]. The mental disturbances usually persist for 6-7 h after administration of the compound, i.e., so long as traces of it remain in the body [8].

It is therefore interesting to study changes in the brain during prolonged adminstration of lysergide (LSD), and also their reversibility. No such investigations were found in the accessible Soviet and Western literature.

In a previous investigation, changes in the rat brain were studied during prolonged (4 weeks) administration of lysergide. Marked changes of a degenerative character were found in the neurons, in the form of acute swelling with increased intensity with an increase in the duration of poisoning. The most marked changes were observed in the ganglionic cells of the cortex, thalamus, and hypothalamus. Changes were also found in the RNA and DNA content, with inhibition of synaptic communication and of glial reactions.

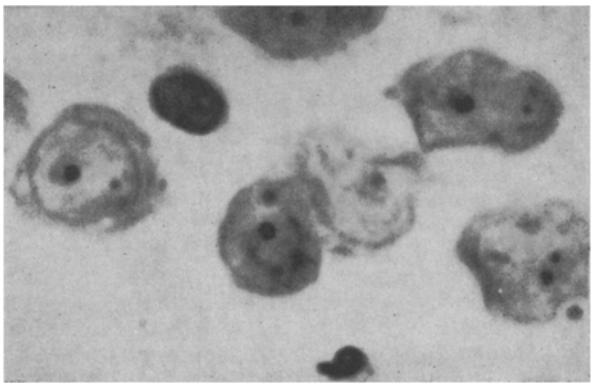

Fig. 1. Greatly enlarged nucleoli with large chromatin granules in neurons of the lateral nucleus of the thalamus. Nissl, 600×.

The object of the present investigation was to determined the reversibility or otherwise of the changes in the rat brain after the end of prolonged lysergide poisoning.

EXPERIMENTAL METHOD

Lysergide (Lysergamide, Czechoslovakia) was injected intramuscularly in a dose of 40 μg/kg daily for 4 weeks into 100 male albino rats aged 3 months. The animals were sacrificed (25 at each time) 1, 2, 3, and 4 weeks after the end of poisoning. Frontal brain sections were taken at the level of the optic chiasma, the tuber cinereum, the cerebral peduncles, the floor of the fourth ventricle, and the inferior olive in the medulla for histological investigation.

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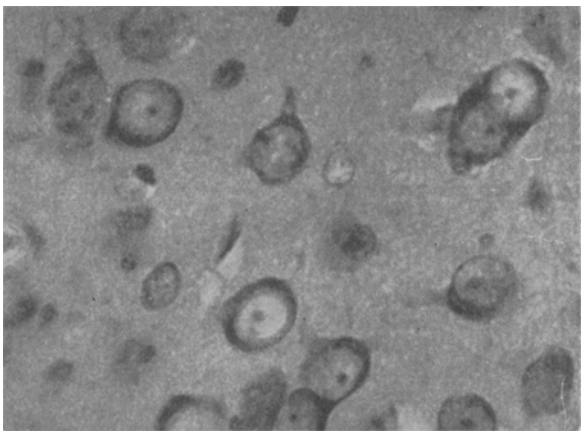

Fig. 2. Binuclear cells in deep layers of the cortex. Nissl, 600×.

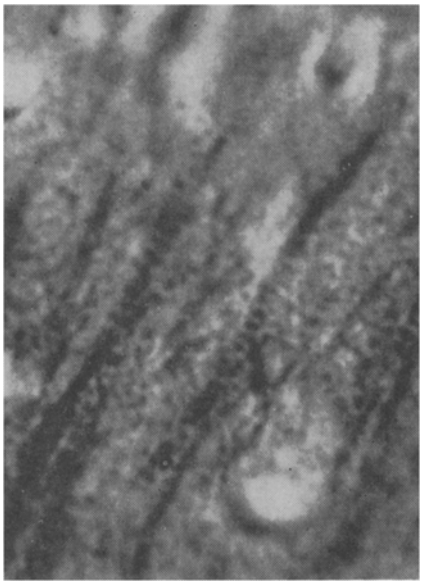

Fig. 3. Modified spines on apical dendrites of cortical pyramidal cells. Golgi–Deineka, 1800×.

EXPERIMENTAL RESULTS

The histological analysis showed that the first signs of readaptation did not appear until the seventh day after the end of poisoning. These signs included gradual recovery of the staining properties of the neurons, which were sharply modified in chronic poisoning. Besides a homogeneous state of the cytoplasm, in many nerve cells of the cortex, thalamus, hypothalamus, and caudate and lentiform nuclei, the tigroid began to appear finely granular in structures, especially in the apical regions and on the membrane. The nucleoli were increased in size, darkly stained, and contained chromatin granules, while in some neurons they also contained compact structures resembling crystalloids (Fig. 1).

The reaction for RNA became more marked. RNA appeared as tiny granules or as clearly stained and homogeneous, thin bands on the membrane. The nucleoli were clearly and brightly stained. Different types of interneuronal connections became more clearly visible. However, only a few synaptic endings were visible, especially on the ganglionic cells of the cortex.

At the end of the second week binuclear cells were observed, mainly in the deep layers of the cortex. They were frequently surrounded by satellites (Fig. 2). The most definite signs of readaptation were found at the end of the third and, in particular, at the fourth week. At this stage the staining properties of the neurons were very well developed. The tigroid was clearly visible in the cytoplasm, and its intensity of staining was actually slightly increased. The signs of central acidophilia, observed during the first 2 weeks, had disappeared. Both apical and basal dendrites were again clearly distinguishable. The number of spines on them, especially on the apical dendrites, was considerably increased. The spines appeared coarse (Fig. 3).

Increased interneuronal activity could be judged from the increased number of interneuronal connections and of synaptic endings. The recovery of reactivity of all forms of glial cells, especially the oligodendroglia, was a conspicuous feature. As traces of the previous neurotoxicosis, leading to death of individual neurons or groups of them, at all stages of recovery a disturbance of the cytoarchitectonics could be observed; this took the form of small foci of complete absence or a decrease in the number of cells in layers III-V of the cortex.

The reaction of the blood vessels and meninges must next be considered. By the end of the fourth week of poisoning with lysergide the walls of the vessels appeared thickened, with evidence of seepage of plasma, and the meninges were edematous and swollen. Their readaptation took place slowly. These changes were still observed to a slight degree at the end of the first and second weeks of recovery period. In the third and fourth weeks, some increase in thickness of the meninges and blood vessel walls of the brain could be seen, together with an increase in the number of cells, indicating the initial signs of fibrosis.

The changes produced by chronic administration of lysergide were thus persistent and recovery from them virtually did not begin until the third week after the end of administration of the drug. The onset of recovery was reflected by the reaction of the nucleolus, the appearance of Nissl granules in the cytoplasm,

and an increase in their staining properties. This is in agreement with the views of Western observers [3-7], who regard these phenomena as a compensatory reaction of the neurons. A characteristic feature of the reaction of the nucleolus in the recovery period after the end of lysergide poisoning is the appearance of basophilic granules and crystalloids in it. This occurs in those parts of the brain where the neurons have suffered most from the poisoning (cortex, thalamus, hypothalamus).

The appearance of binuclear cells at the end of the third week of the recovery period in certain parts of the cortex and thalamus is noteworthy. Some workers [1, 2] regard the presence of binuclear and polynuclear neurons in the nervous system as a sign of reparative regeneration of the nerve tissue. Characteristically, binuclear cells were found in the period of active readaptation when all forms of functional activity of the neurons were becoming accentuated. It must be emphasized that this was accompanied by an increase in the number of astrocytes, oligodendrocytes, and microgliocytes, whose reactivity was depressed by the lysergide poisoning. The increase in glial reactivity was interpreted as a sign of readaptation.

It is concluded that the greater part of the changes produced in the brain of experimental animals by prolonged administration of lysergide are evidently reversible in character. At the same time, the existence of residual phenomena in the form of foci of disappearance or a decrease in the number of cells in certain layers of the cortex, thalamus, and hypothalamus, and the tendency toward fibrosis of the vessel walls and meninges must be regarded as evidence of changes leading to some disturbance of normal brain activity.

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