HISTOTOPOGRAPHY OF CHANGES IN BRAIN ENZYME ACTIVITY PRODUCED BY FLUPHENAZINE IN RATS

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Fluphenazine in doses of 1 and 5 mg/kg reduced the activity of respiratory enzymes (succinate, isocitrate, NAD · H_2, and NADP · H_2 dehydrogenases) in various brain structures of rats 3 h after a single subcutaneous injection; the most marked changes in enzyme activity were observed in the limbic and frontal regions of the cortex.

KEY WORDS: fluphenazine; enzymes; brain.

Neuroleptics have a marked influence on the energy metabolism of the brain [5-7]. However, the degree of enzymic changes in the various structures and nuclei of the brain produced by the action of neuroleptics still awaits differential analysis.

This paper gives the results of a study of the histotopography of some respiratory enzymes in the rat brain during administration of fluphenazine, one of the most effective of neuroleptics.

EXPERIMENTAL METHOD

Thirty male albino rats weighing 180-200 g were used. The rats were decapitated 3 h after a single subcutaneous injection of fluphenazine in doses of 1 or 5 mg/kg (when the greatest changes occur in the activity of the brain dehydrogenases [4]) and activity of succinate, isocitrate, NAD · H_2, and NADP · H_2 dehydrogenases were determined histochemically [1, 3] in cryostat sections (20 μ) of the brain.

EXPERIMENTAL RESULTS AND DISCUSSION

Fluphenazine, in a dose of 1 mg/kg, caused a decrease in the activity of succinate, isocitrate, NAD · H_2, and NADP · H_2 dehydrogenases in many brain structures (Fig. 1).

Marked inhibition of respiratory enzyme activity was observed in the neurons and glial cells of the anterior and middle zones of the limbic cortex (L), chiefly in layers I-III; changes were slight in the posterior zones of the limbic cortex. A moderate decrease in dehydrogenase activity was observed in the frontal cortex — the frontal zone proper and the posterior frontal (FP) area, the lateral septal nuclei (LS), the superior colliculus (CS), and in the region of the raphe (R) of the medulla; the most sensitive structure in the septum was the lateral nucleus and in the superior colliculus the gray surface layer. Changes in the region of the raphe were localized chiefly in processes of the nerve cells and the cytoplasm of the small neurons, whereas enzyme activity was only very slightly reduced in the large and medium-sized reticular cells. A slight decrease in dehydrogenase activity was observed in the parietal cortex (P), mainly in its superior association layers, the midline nuclei of the thalamus (the parvocellular part of the medio-dorsal nucleus — MD, the

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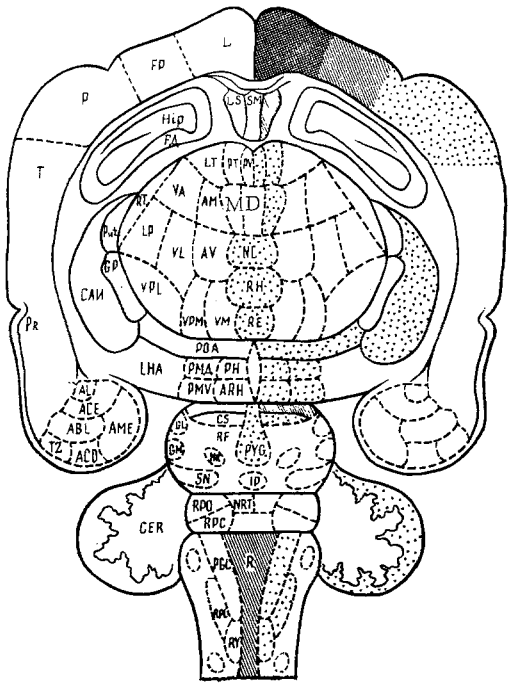

Fig. 1. Effect of fluphenazine on activity of succinate, isocitrate, NAD · H_2, and NADP · H_2 dehydrogenases in the rat brain. Identification of structures in text. Cross hatching) marked decrease in activity; oblique shading) moderate decrease; dots) slight decrease in enzyme activity.

centrum medianum — NCM, and the nucleus rhomboideus — RH and nucleus reuniens — RE), in the paraventricular (PV) and parathenial (PT) nuclei, in the preoptic area (POA), in the medial zone of the posterior hypothalamus (dorsal premammillary — PMD, ventral premammillary — PMV, arcuate — ARH, and posterior — PH nuclei), the caudate nucleus (CAU), the central gray matter (PVG), the molecular layer of the cerebellar cortex (CER), and in some nuclei of the medullary reticular formation (gigantocellular — PGC, parvocellular — RPC, and ventral — PV reticular nuclei). In a dose of 5 mg/kg, fluphenazine caused similar changes in enzyme activity, except in the region of the frontal cortex (FP), where the inhibitory effect of the drug was considerably stronger.

It was interesting to compare the effects of fluphenazine and of the classical neuroleptic chlorpromazine. Previous investigations [3, 4] showed that chlorpromazine, if given as a single dose of 1.5 and 20 mg/kg, reduces activity of succinate, isocitrate, NAD · H_2, and NADP · H_2 dehydrogenases in various structures of the rat brain. The histotopography of the enzymic changes produced by chlorpromazine and fluphenazine shows wide agreement although there were certain differences. For instance, chlorpromazine (5 mg/kg), unlike fluphenazine (5 mg/kg), also lowered the dehydrogenase activity in a large part of the neocortex, including parts of the temporal (T) and piriform (PR) cortex, the hippocampus (Hip), the medial and lateral thalamic nuclei (AM, AV, VM, VPM, VL, VPL, LP, VA, LT), the striopallidary complex (CAU, GP, Put), certain nuclei of the amygdala (ACE, ABL, AME), the lateral hypothalamic areas (LHA), geniculate bodies (GL, GM), the mesencephalic reticular formation (RF), the interpeduncular nucleus (IP), and pontine nuclei (RPO, NRT, RPC). The action of chlorpromazine is thus virtually total in character. In some brain formations, notably hypothalamic nuclei, the inhibitory effect of chlorpromazine is much stronger than that of fluphenazine. Fluphenazine has almost maximal action in a dose of 1 mg/kg whereas chlorpromazine produces its greatest inhibitory effect in doses of 5-20 mg/kg.

The most sensitive parts of the brain to the action of fluphenazine were the anterior zones of the limbic cortex and the frontal region of the neocortex. In its effect on dehydrogenases in these parts of the brain fluphenazine surpasses chlorpromazine and trifluoperazine [4]. The frontal zones of the cortex are known to be responsible for highly complex forms of programming, regulation, and control of human conscious activity. A no less important role in the integration of behavioral and emotional responses is played by the anterior zones of the limbic cortex. The possibility cannot be ruled out that the influence of neuroleptics on these parts of the cortex is an important factor in the mechanism of their psychotropic action. A definite decrease in respiratory enzyme activity in the limbic and frontal cortex may be accompanied by manifestations of hypoxia, leading to reduced functional activity of these formations. The development of the depriming effect of chlorpromazine in the frontal lobes is confirmed by electrophysiological investigations in psychiatric patients [2]. The histotopographical features of the inhibitory effect of fluphenazine on the oxidative enzymes of the brain are interesting from the standpoint of selectivity of action of the drug. The further study of psychotropic agents from this point of view and comparison of the results with those of electrophysiological, neurochemical, and other investigations would make a very important contribution to the identification of the mechanism of action of this group of drugs.

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