HISTOCHEMICAL EFFECTS OF FLUACIZINE ON FLAVIN DEHYDROGENASE ACTIVITY IN THE RAT BRAIN

V. A. Markin and V. S. Mitrofanov

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The effect of the new psychotropic drug fluacizine on the activity and distribution of flavin dehydrogenases was studied in the rat brain by histochemical methods. After a single injection, fluacizine caused a moderate or slight decrease in activity of the enzymes in many brain structures. In a long-term experiment, besides reducing enzyme activity, the drug also led to definite activation of the flavin dehydrogenases in some parts of the cortex and subcortex.

Fluacizine [10-(β-diethylaminopropionyl)-2-trifluoromethylphenothiazine hydrochloride] is a new and original psychotropic drug synthesized in the Institute of Pharmacology, Academy of Medical Sciences of the USSR, by S. V. Zhuravlev and A. N. Gritsenko. Experimental (Yu. I. Vikhlyaev et al.) and clinical (G. Ya. Avrutskii et al.) investigations have shown that fluacizine possesses a well-marked antidepressive action and can abolish the extrapyramidal disorders developing during neuroleptic therapy.

The paper describes the results of a histochemical study of the effect of fluacizine on the activity and distribution of some flavin dehydrogenases in structures of the rat brain.

EXPERIMENTAL METHOD

Experiments were carried out on 200 noninbred male albino rats weighing 180-200 g. Fluacizine was injected subcutaneously as single doses of 1, 5, 20, and 50 mg/kg or repeatedly in doses of 10 mg/kg (once daily) for 7, 15, and 30 days. Animals of the control group were injected with 1 ml physiological saline. When a single injection of fluacizine was given, the brain was studied after 1, 3, and 24 h, and when the drug was given repeatedly the brain was examined 3 and 24 h after the last injection. Freshly frozen brains of the control and experimental rats were combined into tissue blocks. Brain sections, 20 μ in thickness, were cut in a cryostat at −10° C. Activity of the following flavin dehydrogenases was studied: succinate dehydrogenase by the method of Nachlas et al. [5], NAD·H_2 dehydrogenase (DPN·H-diaphorase, NAD·H_2-tetrazonium oxidoreductase) and NADP·H_2 dehydrogenase (TPN·H-diaphorase) by the method of Scarpelli et al. [6], and mitochondrial α-glycerophosphate dehydrogenase (α-GPD) by the method of Nachlas et al. [5], with the addition of coenzyme Q to the incubation medium [7].

EXPERIMENTAL RESULTS

The histochemical tests showed that fluacizine, in doses of 5, 20, and 50 mg/kg, lowered the activity of these respiratory enzymes in many brain structures 3 h after a single injection. The inhibitory effect of fluacizine was seen most clearly when it was given in doses of 20 and 50 mg/kg, but only very slightly in a dose of 1 mg/kg. The experimental results indicate differences in sensitivity of the flavin dehydrogenases to the action of the drug. The greatest decrease was observed in the activity of succinate dehydrogenase and NAD·H_2 and NADP·H_2 dehydrogenases. Activity of the mitochondrial α-GPD was reduced to a lesser degree.

Morphology Group, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow.
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Fluacizine, in doses of 20 and 50 mg/kg, caused a moderate decrease in activity of the flavin enzymes in the limbic cortex, nonspecific thalamic nuclei, preoptic region, lateral nuclei of the septum and grisea centralis, posterior hypothalamus, superior colliculi, and medullary reticular formation. The decrease in enzyme activity in the hippocampus, frontal cortex, and nucleus interpeduncularis was slight. In the region of the parietal, temporal, and insular cortex, the amygdala, caudate nucleus, and putamen, these changes were inconstant, and in some rats a slight increase in enzyme activity was found in these structures. No changes were found in the ventrolateral nuclei of the thalamus, the subthalamic nucleus, globus pallidus, geniculate bodies, mesencephalic reticular formation, substantia nigra, red nucleus, or cerebellar cortex.

It will be noted that the histochemical changes were most marked in the tissues of the limbic structures such as the limbic cortex, central thalamus, septum, preoptic region, and grisea centralis. The decrease in enzyme activity in these structures was observed both in nerve cells and in the intercellular substance, and in the limbic cortex changes were found mainly in the anterior and middle areas (V. M. Svetukhina's atlas [2]) and in the cells of layers II and V. In the septal region, mainly the lateral nuclei reacted, and in the grisea centralis, mainly the medial zone.

The activity of these enzymes was partially restored 24 h after a single injection of fluacizine in a dose of 5 mg/kg. In animals receiving the compound in doses of 20 and 50 mg/kg, only a tendency toward recovery of enzyme activity was observed.

After prolonged administration of fluacizine in a dose of 10 mg/kg, some increase in its inhibitory effect on the flavin dehydrogenases was observed compared with the changes taking place after a single dose, but the localization of histochemical changes was almost the same. In the parietal cortex, amygdala, caudate nucleus, and putamen a definite increase in enzyme activity was revealed by comparison with the controls. A somewhat smaller increase in dehydrogenase activity was observed in the insular and temporal cortex.

These changes were most marked after administration of fluacizine for 2 weeks. The histochemical pictures in these cases was not substantially different if the animals were tested 3 or 24 h after the last injection of the compound.

Inhibition of flavin dehydrogenase activity after single and repeated injections of fluacizine corresponds to published data indicating the characteristic ability of phenothiazine derivatives to inhibit enzymes containing a flavin component in their prosthetic group [1, 3, 4, 8].

In this respect, fluacizine is no exception among the phenothiazine derivatives. However, the inhibitory effect of fluacizine on activity of these flavin enzymes, connected with the respiratory chain of the mitochondria, is moderate or weak in character.

The psychosedative properties of fluacizine, which are characteristic of the neuroleptics, are probably due to initial inhibition of energy processes in the brain by the action of the compound.

As was mentioned previously, an inconstant effect, i.e., no change, a very slight decrease, or even an increase in enzyme activity, was observed in the parietal, temporal, and insular cortex, and also in the amygdala, caudate nucleus, and putamen following injection of a single dose of the drug. However, on repeated administration of fluacizine, a clear increase in activity of the enzymes was observed in these structures. This fact, together with the partial adaptation of the dehydrogenases in the limbic and frontal cortex, central thalamus, hypothalamus, and other structures can be regarded as compensatory reactions. Activation of the enzymes in the parietal, temporal, and insular regions of the cortex and amygdala probably plays an important role in the antidepressive action of fluacizine. The increase in enzyme activity in the caudate nucleus and putamen is evidently related to the corrective effect of fluacizine on extrapyramidal disorders induced by neuroleptics. A preliminary assessment of the results does not rule out other possible explanations of the mechanism of action of fluacizine.

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