SELECTIVE ACTION OF THE NEW ANTIDEPRESSANT FLUACIZINE ON PYRIDINE DEHYDROGENASE ACTIVITY IN THE RAT BRAIN

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The effect of the new Soviet antidepressant fluacizine, with a phenothiazine type of structure, on activity of NAD-dependent dehydrogenases in different parts of the rat brain was investigated histochemically. A single injection of fluacizine reduces the activity of oxidative enzymes preferentially in certain parts of the limbic system and medullary reticular formation. After repeated injections of the drug, the above effect is joined by activation of dehydrodrogenases in some parts of the cortex, striopallidum, amygdala, and hippocampus.

An earlier investigation [4] showed that fluacizine can exert not only an inhibitory, but also an activating effect on the flavine dehydrogenases in the structures of the rat brain. It was therefore decided to study the action of the compound on the activity of another group of oxidative enzymes – the pyridine dehydrogenases, important in the energy metabolism of the brain.

EXPERIMENTAL METHOD

Experiments were carried out on 220 noninbred male albino rats weighing 180-200 g. Fluacizine was injected subcutaneously in single doses of 1, 5, 20, and 50 mg/kg and repeatedly (once daily) in a dose of 10 mg/kg for 7, 15, and 30 days. The animals of the control group received 1 ml physiological saline. The brain was examined 1, 3, and 24 h after the single dose of fluacizine and 3 h after the last injection of the compound when given repeatedly. In addition, the brain of some animals receiving fluacizine for 15 days was studied 7 days after the last injection. Freshly frozen (with CO_2 gas) juxtaposed tissue blocks of the brains of the experimental and control rats were used. Brain sections 20 μ in thickness were cut in a cryostat at −10°C. Activity of the following NAD-dependent dehydrogenases was investigated (by the method of Hess et al. [5] in Pearse's [6] modification): glutamate dehydrogenase (GDH), lactate dehydrogenase (LDH), isocitrate dehydrogenase (IDH), malate dehydrogenase (MDH), and α-glycerophosphate dehydrogenase (α-GPDH). The intensity of enzyme activity was determined from the number of diformazan grains precipitated and was assessed conventionally as high, medium, and low.

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments showed that fluacizine, 1 and 3 h after single doses of 1 and 5 mg/kg, has a weak and inconstant effect on the activity of the oxidative enzymes studied.

The dominant effect 3 h after administration of single doses of 20 and 50 mg/kg fluacizine was a decrease in the dehydrogenase activity of several brain structures, most marked in certain parts of the limbic system and in the medullary reticular formation (Table 1). The histochemical changes were moderately severe, and GDH, IDH, and MDH reacted more distinctly than LDH and α-GPDH to administration of fluacizine. The pyridine dehydrogenases were thus somewhat less sensitive to fluacizine than the flavine dehy-

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TABLE 1. Changes in Activity of NAD-Dependent Dehydrogenases (GDH, IDH, MDH, LDH, and α-GPDH) in the Brain of Rats under the Influence of Fluacizine

Parts of the brain	Dose of compound					
	1 and 5 mg/kg		20 and 50 mg/kg		10 mg/kg	
	3 h	24 h	3 h	24 h	15 days	7 and 30 days
Anterior and posterior parts of the limbic cortex, central thalamus, lateral nuclei of the septum, central gray matter, superior colliculi, posterior hypothalamus	–	no change	– –	no change	– –	–
Medullary reticular formation	–	no change	–	– –	– –	–
Posterial parts of limbic cortex, frontal cortex, preoptic region, medial and anterior groups of thalamic nuclei, interpeduncular nucleus, cerebellar cortex	(–)	no change	–	no change	(–)	no change
Parietal cortex, amygdala, caudate nucleus	no change	no change	(+)	no change	+ +	–
Temporal and insular cortex, hippocampus, putamen, globus pallidus, mesencephalic reticular formation	no change	no change	(+)	no change	+	no change
Specific nuclei of the thalamus, anterior hypothalamus, inferior colliculi, geniculate bodies, red nucleus, substantia nigra, motor nuclei of mesencephalon and medulla	no change	no change	no change	no change	no change	no change

Legend: ++) Moderate increase in enzyme activity; +) constant but slight increase; – –) moderate decrease; –) constant but slight decrease; (+) or (–): tendency toward increase or decrease in enzyme activity respectively.

drogenases studied previously [4]. However, the localization of the enzymic changes was the same in both cases. Activity of the pyridine dehydrogenases 24 h after a single dose of fluacizine was completely restored in all structures except the medullary reticular formation (activity of the flavine enzymes was only partly restored at this time).

In certain brain structures (parietal cortex, amygdala, caudate nucleus, hippocampus), 3 h after a single injection injection of fluacizine in doses of 20 and 50 mg/kg, a tendency toward activation of the oxidative enzymes was observed. After repeated administration of fluacizine, a constant, medium increase in dehydrogenase activity was observed in these same structures and also in the insular and temporal cortex. In addition, in some structures (limbic cortex, central thalamus, etc.) fluacizine continued to have an inhibitory effect throughout the experiment. This effect of the compound, like its activating action, was most marked by the end of the 2nd week of the experiment. Activity of these enzymes was fully restored 7 days after the last injection of fluacizine.

The effect of fluacizine on activity of the flavine and NAD-dependent dehydrogenases can instructively be compared with the effect of trifluoperazine (stelazine), because both compounds have a similar chemical structure although they belong to different classes of psychotropic drugs. The writer's earlier histochemical investigations [1-3] showed that trifluoperazine has a marked inhibitory action on activity of the flavine and NAD-dependent dehydrogenases in different parts of the brain, and surpasses fluacizine in this respect. The localization of the enzymic changes observed after a single injection of trifluoperazine and fluacizine is identical, and this is particularly true of structures such as the limbic cortex, the lateral nuclei of the septum, the nonspecific nuclei of the central thalamus, the posterial hypothalamus, the central gray matter, and the medullary reticular formation. Judging by the histochemical changes, fluacizine if given by a single injection behaves as a weak neuroleptic (by contrast with trifluoperazine).

However, if fluacizine is given repeatedly, its ability to activate these oxidative enzymes in various parts of the cortex, the striopallidary system, the amygdala, and hippocampus assumes the leading role.

Clinical trials have shown that fluacizine actively corrects extrapyramidal disorders during neuroleptic therapy. It is therefore important to note that, by contrast with trifluoperazine, fluacizine does not reduce, but increases the dehydrogenase activity in the striopallidum and has a less marked inhibitory effect on the activity of these enzymes in the frontal cortex. The writers consider that the corrective effect of fluacizine is due to its predominant action on the higher levels of the extrapyramidal system, since enzyme activity in its lower levels (the red nucleus and substantia nigra) is almost unchanged by the action of fluacizine.

The antidepressive properties of fluacizine evidently cannot be attributed entirely to its stimulant effect on certain parts of the cortex, amygdala, and hippocampus. The inhibitory action of the compound on certain limbic structures and the medullary reticular formation, similar to the action of neuroleptics, probably plays an important role. In conclusion, it should be noted that prolonged administration of fluacizine (longer than 2 weeks) leads to a decrease in its effect on the activity of these oxidative enzymes.

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