fact, in animals with injury to the rostro-dorsal striatum adaptation to amphetamine is much less marked, whereas after ventral lesions, on the contrary, it is significantly stronger than in the intact group.

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ACTION OF BEFOL AND ITS DERIVATIVES ON MONOAMINE OXIDASE FROM DIFFERENT SOURCES

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Progress in the study of the toxic action of pyridine derivatives, which is important for our understanding of the mechanism of onset of Parkinsonism, has again emphasized the difficulty of studying the biological properties of monoamine oxidases (MAO) [11]. The presence of at least two isozymes, namely MAO of types A and B, in biological objects has been established, and the ratio between them differs even in the same organ of animals of different types, and their physiological role has not yet been explained [14]. Furthermore, multiple forms of MAO, not identical with MAO of types A and B, also exist [9, 10, 12, 13].

In the investigation described below, in order to study the mechanism of action of the new antidepressant befol – *p*-chloro-N-(2-morpholinobutyl)benzamide [4] – its action on MAO of tissues containing different amounts of the A and B isozymes (bovine and rat brain, human placenta and platelets) was investigated and the antimonoamine-oxidase activity of various benzamide derivatives similar to befol also was compared.

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TABLE 1. Effect of Benzamide Derivatives (100 μM) on MAO Activity of Rat Brain Homogenate

Control	Residual MAO activity (percent)			
	serotonin	dopamine	tyramine	2-phenylethylamine
Control	100	100	100	100
Moclobemide	0	92	84	100
Befol	31	90	86	66
LIS-641	139	130	73	100

Legend. Arithmetic mean values based on results of 4-8 parallel experiments. Mean errors do not exceed 10% of arithmetic mean.

TABLE 2. Effect of Befol (100 μM) on MAO Activity (in percent) of Mitochondrial Fractions and Homogenates

Test object	Residual serotonin deaminase activity
Rat brain	
mitochondria	60,7±4,4
homogenate	39,2±3,1
Human placenta:	
mitochondria	79,3±1,4
homogenate	67,0±2,1

Legend. Arithmetic mean values ± mean errors of arithmetic mean, based on results of four parallel experiments.

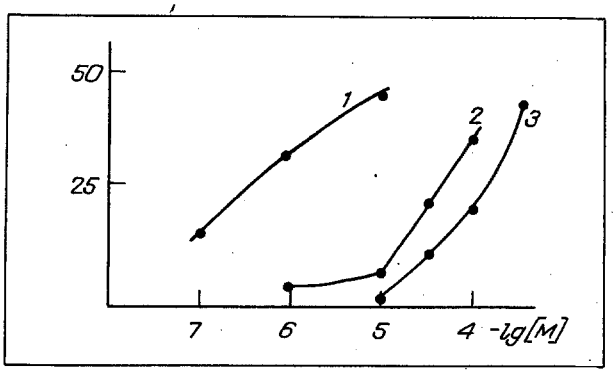

Fig. 1. Inhibition of serotonin-deaminase activity in mitochondria from bovine brain (1), rat brain (2), and human placenta (3) by various concentrations of befol. Abscissa, befol concentration; ordinate, degree of inhibition (in percent of control).

EXPERIMENTAL METHOD

The following were used as sources of MAO activity – 50% rat brain homogenate prepared in 0.01 M K-Na-phosphate buffer (pH 7.6), mitochondrial fractions of rat and bovine brain [5], and human placenta and blood platelets [2].

MAO activity was determined by measuring ammonia released into the incubation sample with an optimal serotonin concentration [5], or release of benzaldehyde, measured spectrophotometrically after extraction from the incubation samples containing benzylamine, with hexane [2], and by a modified radiometric method with serotonin as the substrate [6]. Activity in the absence of inhibitor was taken as 100%.

Moclobemide — *p*-chloro-N-(2-morpholinoethyl)benzamide — was resynthesized, and LIS-641 — *p*-chloro-N-(2-morpholinopropyl)benzamide and befol [1] were synthesized at the Institute of Pharmacology, Academy of Medical Sciences of the USSR.

EXPERIMENTAL RESULTS

The relationship between the length of the carbon chain connecting the aromatic nuclei in the molecule of the inhibitor and the sensitivity of MAO activity to these inhibitors was studied in experiments with MAO from rat brain homogenate. It was shown that mainly serotonin-deaminase activity, characteristic of MAO type A, was inhibited by befol (Table 1). Lengthening the carbon insert from 2 (moclobemide) or 3 (befol) to 4 CH_2-groups (LIS-641) led to loss of the inhibitory effect or even to some degree of activation of the enzyme. Inhibition of 2-phenylethylamine-deaminase activity, characteristic of MAO type B, was less marked. This phenomenon was observed also when dopamine- or tyramine-deaminase activity, characteristic of both types A and B of MAO was investigated.

Inhibition of MAO activity by moclobemide is known to be stronger in vivo than in vitro [7, 8]. It has been suggested that the moclobemide molecule undergoes modification in the body, and only after that is activity of type A MAO truly blocked [7, 8]. This phenomenon may evidently also explain our own data (Table 2), according to which befol inhibits type A MAO activity to a somewhat greater degree in tissue homogenates than in mitochondrial fractions isolated from them.

The action of befol on MAO from various sources, containing both predominantly MAO type A (human placenta) and both types of MAO (bovine and rat brain), or only type B MAO (human platelets) was studied in more detail.

Dependence of inhibition of serotonin-deaminase activity of MAO on befol concentration (Fig. 1) indicates differences in the sensitivity of MAO from different biological objects to the inhibitory effect of befol. MAO from bovine brain was found to be most sensitive to the inhibitory action of befol, by contrast with human placenta. As might be expected, platelet MAO, within the concentration range from 10^{-8} to 10^{-5} M, is not inhibited by befol if its activity is determined with benzylamine as the substrate.

The results of these experiments are in agreement with data in the literature. Moclobemide, like befol, possesses the properties of a selective inhibitor of type A MAO [7, 8]. Information is available on differences in sensitivity to the action of selective inhibitors depending on organ-dependent and species-dependent characteristics of MAO [3]. These data together with our own results described above are evidence of the great variability of the properties of type A MAO in different species.

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