INHIBITION OF MONOAMINE OXIDASE ACTIVITY BY ANTIHISTAMINES OF THE SELENOPHENE CLASS

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Antihistamines of the selenophene class inhibit mitochondrial monoamine oxidase activity of rat liver in vitro, selectively blocking deamination of several biogenic monoamines. A small, yet statistically significant inhibition of monoamine oxidase activity in vivo by selenophene was observed in the tissues of the kidneys and liver (but not the brain) of rats.

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The selenophenes possess antihistamine activity and prolonged action [4-7], potentiating some effects of noradrenalin and adrenalin, substrates of monoamine oxidase (MAO). Some antihistamines (diphenylamine, phenethazine, and methapheniline) inhibit MAO activity [8-10].

In the present investigation the anti-MAO activity of the following selenophenes (synthesized at Moscow University by M. A. Gal'bershtam and Yu. K. Yur'ev) was studied: N_1N-dimethyl-N'-phenyl-N'-(selenenyl-2)-ethylenediamine hydrochloride (preparation No. 1); N_1N-dimethyl-N'-(α-pyridyl)-N'-(selenenyl-2)-ethylenediamine hydrochloride (preparation No. 4); N_1N-dimethyl-N'-(α-pyridyl)-N'-(5-chloroselenenyl-2)-ethylenediamine hydrochloride (preparation No. 5), and N_1N-dimethyl-N'-(α pyridyl)-N'-(5-bromoselenenyl-2)-ethylenediamine hydrochloride (preparation No. 6).

EXPERIMENTAL METHOD

Mitochondria were isolated from a 10% rat liver homogenate as described previously [2]. MAO activity was determined [1-3] by liberation of ammonia during incubation of lyophilized mitochondria (6-10 mg) with saturating concentrations of tyramine hydrochloride (6 μmoles), serotonin creatinine-sulfate (10 μmoles), dopamine hydrochloride (6 μmoles), or noradrenalin hydrotartrate (2 μmoles).

In the experiments in vivo, selenophenes were injected intravenously in a dose of 28 mg/kg into male albino rats weighing 150-180 g. MAO activity was determined 2, 3, 5, 18, 48, and 72 h later in 50% homogenates of the liver, kidneys, and brain prepared in a 2.5% solution of the detergent OP-10 in 0.2 M phosphate buffer, pH 7.45. The protein content was determined by the Kjeldahl method.

EXPERIMENTAL RESULTS

Preparations Nos. 1, 5, and 6 were found to be powerful inhibitors of tyramine deamination, while No. 4 was a weak inhibitor (Fig. 1). Pharmacological tests showed that Nos. 5 and 6 were the most active antihistamines, and Nos. 4 and 1 the least active. The most active inhibitors of deamination of noradrenalin, dopamine, and serotonin were preparations Nos. 5 and 6; No. 4 was less active, and No. 1 possessed even weaker inhibitory action on MAO activity (Fig. 1). Preparations Nos. 5 and 6 inhibited deamination of tyramine and dopamine most strongly, but inhibited deamination of serotonin only slightly.

Preincubation at room temperature of suspensions of rat liver mitochondria with preparations Nos. 5 or 6 for different times (from 1 to 60 min) before addition of tyramine or serotonin did not increase inhibition. Dialysis (24 h, including 4 h on magnetic mixer, against 330 volume of 0.1 M phosphate buffer, pH 7.45) of the enzyme preparation treated with selenophene No. 6, added in a concentration necessary to in-

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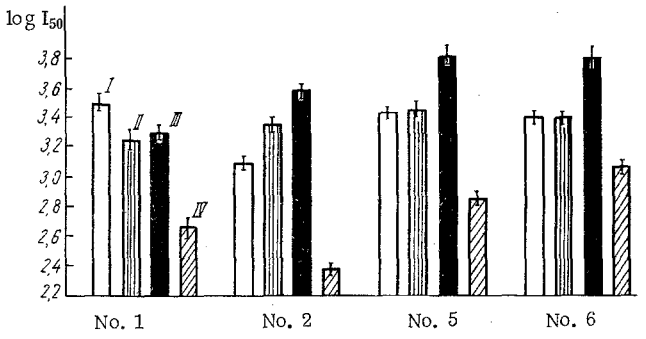

Fig. 1. Effect of selenophenes on deamination of some biogenic monoamines by mitochondrial MAO from rat liver. Ordinate, values (M±m from results of 4-6 experiments) of negative logarithms of concentrations of inhibitors needed to inhibit deamination of amines by 50%; abscissa, serial No. of preparation. I) Tyramine; II) dopamine; III) noradrenalin; IV) serotonin.

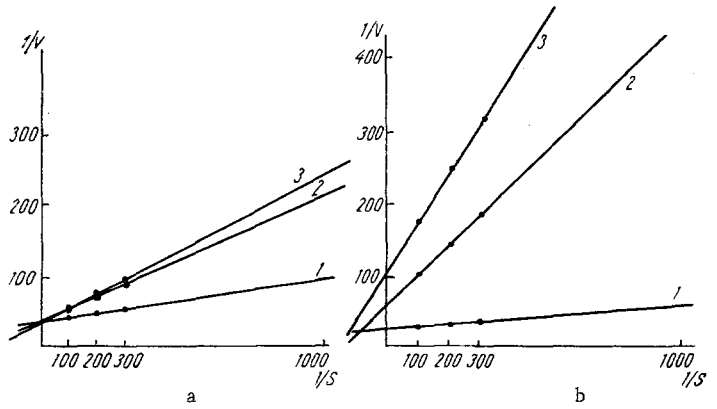

Fig. 2. Character of inhibition of enzymic deamination of serotonin (a) and tyramine (b) by preparations No. 5 (3) and No. 6 (2). 1) Control without inhibitors; results plotted on graph by the double reciprocal method of Lineweaver and Burk [9].

TABLE 1. Relationship between Dissociation Constants (K_i) of Enzyme-Inhibitor Complex and Nature of Substrate

Inhibitor (preparation No.)	Substrate	
	tyramine	serotonin
5	$3.6 \cdot 10^{-4}$	$4 \cdot 10^{-3}$
6	$3.8 \cdot 10^{-4}$	$6.5 \cdot 10^{-3}$

hibit deamination of tyramine by 90-100%, led to a decrease in inhibition of deamination of this amine by 40-60%. In analogous experiments with serotonin as substrate, complete abolition of the inhibitory action of preparation No. 6 was observed, indicating that the action of the inhibitor is reversible.

Addition of increasing concentrations of tyramine ($5 \cdot 10^{-4}$-$1 \cdot 10^{-2}$ M) to samples containing preparations Nos. 5 or 6 did not diminish the inhibitory action of the selenophenes (Fig. 2a). After addition of serotonin in increasing concentrations ($5.5 \cdot 10^{-3}$-$2.2 \cdot 10^{-2}$ M) a decrease in the inhibitory action of these preparations was observed (Fig. 2b). Hence, preparations Nos. 5 and 6 are competitive inhibitors of serotonin deamination but noncompetitive inhibitors of tyramine deamination.

From the results showing the character of action of these inhibitors, dissociation constants (K_i) of the enzyme-inhibitor complex were calculated for preparations Nos. 5 and 6 (Table 1). In experiments in vivo, a slight (but statistically significant, $P < 0.002$) inhibition of deamination of monoamines in the kidneys

(16±6.3%; substrate tyramine) and in the liver (6.4±0.7%; substrate tyramine), but not in the brain tissues (substrates tyramine and serotonin) was observed 2, 3, 5, 18, and 48 h after intravenous injection of preparation No. 6 (28 mg/kg) into rats.

In vivo a small, yet statistically significant inhibiton of MAO activity by preparation No. 6 was found. Repeated injections of preparation No. 6 for several days did not potentiate the inhibition.

The view that the selenophenes may become bound to plasma or tissue proteins was not confirmed by special experiments. Likewise no appreciable difference could be found between the degree of inhibition of MAO activity of rat liver by selenophene No. 6 in sections, homogenates, or suspensions of mitochondria carefully purified from soluble ballast proteins by washing with hypotonic phosphate buffer [2].

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