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EFFECT OF PYRAZIDOL AND DEPRENIL ON RAT INTESTINAL MONOAMINE OXIDASE

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UDC 612.015.1:577.152.143]-064:615.214.32

KEY WORDS: monoamine oxidase; pyrazidol; deprenil.

Pyrazidol,* which has characteristic properties of antidepressants, as was shown previously inhibits the deamination of various tissue amines of the rat liver and brain [1]. The drug has been successfully used in clinical practice for the treatment of patients with various forms of depression [2].

Blocking of intestinal monamine oxidase (MAO) by the therapeutic use of its inhibitors may give rise to the so-called cheese syndrome, manifested as severe disturbance of the hemodynamics [5]. The biological role of intestinal MAO is evidently connected with the detoxication of toxic amines entering the blood stream from the intestine. Nowadays MAO of types A and B are distinguished. It is considered that human and rat intestinal MAO consists of type A [5, 8].

The object of this investigation was to study the effect of pyrazidol and deprenil on MAO activity in the mitochondrial fraction of the rat intestine.

EXPERIMENTAL METHOD

Noninbred male albino rats weighing 180-200 g were used. The mitochondrial fraction was sedimented at 8500g from a 10% tissue homogenate in 0.25 M sucrose solution after separation of the nuclei at 600g. The residue of mitochondria was washed with 7.5 mM phosphate buffer, pH 7.4, suspended in the same buffer (5 mg protein/ml), and solubilized with Triton X-100 (final concentration 1%). To determine MAO activity, usually 4 mg protein of the solubilized mitochondrial suspension was added to the samples. The method of determination of MAO activity based on liberation of ammonia, the sources of the chemical compounds used, and their characteristics were described previously [4]. Substrates were used in the following optimal concentrations, determined in separate experiments: tyramine 7.9 mM; serotonin 8.9 mM; 2-phenylethylamine 0.39 mM.

EXPERIMENTAL RESULTS

Data on inhibition by pyrazidol of the deamination of various amines by intestinal mito-

*1,10-trimethylene-3-methyl-1,2,3,4-tetrahydropyrazino(1,2-a)indole hydrochloride.

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0007-4888/81/9103-0317$07.50

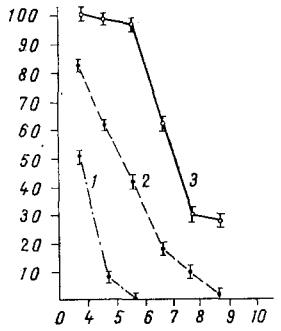

Fig. 1

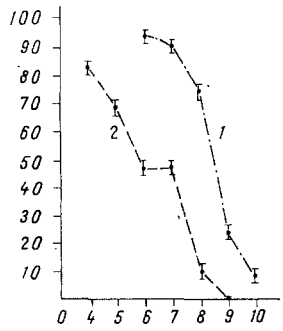

Fig. 2

Fig. 1. Inhibition of rat intestinal MAO by pyrazidol. Samples of 1.8 ml contained solubilized intestinal mitochondria, 0.05 M phosphate buffer, pH 7.4, various concentrations of pyrazidol, and one of the substrates. Mean values given for deamination of 2-phenylethylamine (1), tyramine (2), and serotonin (3) from three experiments. Here and in Fig. 2: abscissa, log of concentration of inhibitor (pyrazidol); ordinate, inhibition (in %).

Fig. 2. Inhibition of rat intestinal MAO by deprenil. Suspension of solubilized intestinal mitochondria in 0.05 M phosphate buffer, pH 7.4, was preincubated for 40 min at 20°C with different concentrations of deprenil, after which 2-phenylethylamine (1) or tyramine (2) was added in optimal concentrations. Mean results of three to nine experiments shown.

chondria are given in Fig. 1. They show that pyrazidol, in relatively low concentrations (from $5 \cdot 10^{-6}$ to $5 \cdot 10^{-9}$ M), selectively blocks serotonin deamination. In a concentration of $5 \cdot 10^{-6}$ M pyrazidol inhibits serotonin deamination practically completely but has no effect on deamination of 2-phenylethylamine. Only in concentrations 100 times greater ($5 \cdot 10^{-4}$ M) did pyrazidol inhibit the deamination of this amine by 50%. We know [8] that type A MAO is present in the rat intestine. It could therefore be suggested that pyrazidol would inhibit equally the deamination of both serotonin and tyramine. However, concentrations of pyrazidol inhibiting deamination by 50% (I_{50}) differed by almost two orders of magnitude when tyramine and serotonin were used as substrates: $9.5 \cdot 10^{-6}$ M and $1.1 \cdot 10^{-7}$ M, respectively. When the conditions were such that serotonin deamination was practically completely inhibited (Fig. 1: 3), deamination of tyramine (Fig. 1:2) was blocked by only about 40%.

The effect of deprenil, a selective inhibitor of type B MAO [6], on rat intestinal MAO activity also was investigated.

Graphs showing the degree of inhibition of deamination of tyramine and 2-phenylethylamine by intestinal mitochondria as a function of deprenil concentration are given in Fig. 2. It will be clear that MAO sensitive to the action of low concentrations of deprenil is present in rat intestinal mitochondria. The curve of inhibition of deamination of 2-phenylethylamine as a function of deprenil concentration is S-shaped. The corresponding curve when tyramine was used as substrate was biphasic in character, evidence of the presence of the binary MAO system [7]. If only one type of MAO is present in the rat intestine, curves of inhibition of deamination of tyramine and 2-phenylethylamine as a function of deprenil concentration ought to coincide, as has been demonstrated for type B MAO from bovine kidney mitochondria [3]. As the results described above show, the rat intestine contains approximately 50% each of types A and B MAO. Pyrazidol selectively inhibits type A MAO in rat intestinal mitochondria.

Pyrazidol has some degree of organ selectivity, as is clear from a comparison of its effect on MAO from rat brain and intestine. For instance, values of I_{50} for pyrazidol when tyramine was used as substrate were $9.5 \cdot 10^{-6}$ and $1 \cdot 10^{-5}$ M respectively for MAO of rat intestinal and brain mitochondria [1]. In these concentrations pyrazidol inhibits deamination of tyramine by rat liver mitochondria by only 20-25% [1]. The value of I_{50} of pyrazidol for

liver MAO when tyramine was used as substrate was $2.5 \cdot 10^{-4}$ M.

The results thus point to the presence of MAO of types A and B in the rat intestine and indicate that pyrazidol selectivity blocks type A MAO.

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