ACTION OF SOME HYDRAZINE AND AMINOPERHYDROACRIDINE DERIVATIVES ON OXIDATIVE DEAMINATION OF SEROTONIN IN DIFFERENT ORGANS AND IN ANIMALS OF DIFFERENT SPECIES

Z. P. Gureeva

UDC 615.214.32.015.45:[612.018:547.576

Experiments on rats showed that 2-methyl-2-benzoylbenzhydrazide, N,N-dimethyl-α-(P-chlorophenoxy)-β-alanine 2-isopropylhydrazide, and imidazole-4(5)-carboxylic acid 2-isopropylhydrazide inhibit the oxidation of seritonin by liver homogenates to a greater degree than its oxidation by brain homogenates. β-Phenylaminopropionic acid hydrazide, 10-amino-β-perhydroacridine, 10-isopropylamino-α-perhydroacridine, and 10-isopropylamino-β-perhydroacridine inhibit oxidative deamination of serotonin in liver homogenates only and have no action on this process in brain homogenates. Experiments on rats and mice showed that 10-amino-α-perhydroacridine and imidazole-4(5)-carboxylic acid 2-isopropylhydrazide definitely blocked the oxidation of serotonin in rat brain homogenates but did not affect this process in mouse brain homogenates. The compound 2-methyl-2-oylbenzhydrazide mainly inhibits serotonin oxidation in rat brain homogenates, while 4,6-diphenylpyrimidine-2-carboxylic acid 2-isopropylhydrazide and Nialamide, on the other hand, block the inactivation of serotonin in mouse brain homogenates to a greater degree.

The most promising compounds for future clinical use as antidepressants are the monoamine oxidase (MAO) inhibitors, which act selectively on the brain enzyme and to a lesser degree on liver MAO [4, 6]. In the search for MAO inhibitors, comparison of the action of substances on the liver and brain MAO of animals of different species is thus of great interest.

For these reasons, in the investigation described below the effect of hydrazine and aminoperhydroacridine derivatives on the breakdown of serotonin by rat liver and brain homogenates was compared.

In view of reports in the literature that human MAO and MAO of certain species of experimental animals are equally sensitive to blocking agents [1, 2], it was decided to study whether selected inhibitors exhibit species differences in their action on the enzyme.

EXPERIMENTAL

Experiments were carried out on albino rats weighing from 150 to 200 g and albino mice weighing from 19 to 25 g of both sexes. The compounds were injected as aqueous solutions (insoluble compounds were first suspended in 0.1% starch solution). The substances were given in doses of 0.14 LD_{50} for mice. The animals were killed by decapitation 2 and 18 h after administration of the compounds. The organs were homogenized in the cold in twice their volume of 0.2 M phosphate buffer, pH 7.4. MAO activity was judged from the quantity of serotonin (4 μmoles/ml) broken down during incubation with tissue homogenates [3]. Additional extraction of the serotonin by Ozaki's method [5] was carried out in the experiments in vitro. The degree of inhibition of serotonin oxidation (in percent) was expressed as the difference between the quantity of amine destroyed by organ homogenates of the control and experimental animals.

Laboratory of Pharmacology, Novokuznetsk Pharmaceutical Chemical Research Institute, Ministry of the Medical Industry of the USSR. (Presented by Academician of the Academy of Medical Sciences of the USSR S. E. Severin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 74, No. 11, pp. 36-39, November, 1972. Original article submitted April 13, 1971.

TABLE 1. Comparison of Effect of Hydrazine and Aminoperhydroacridine Derivatives on Serotonin Breakdown by Rat Brain (above the line) and Liver (below the line) Homogenates in Experiments in Vivo and in Vitro

Compound	Dose (mg/kg)	Inhibition of serotonon breakdown (%) in vivo				Dose (moles)	Inhibition of serotonin breakdown (%)	
		after 2 h	P	after 18 h	P		in vitro	P
Iproniazid (isonicotinic acid 2-isopropyl-hydrazide)	100	81,8±9,4 (6) 95,5±6,4 (6)	>0,5	95,5±6,4 94,7±4,0	>0,5	5×10^{-4}	64,8±2,7 (6) 56,6±6,0 (4)	>0,5
SOG-7 (β-phenylaminopropionic acid hydrazide)	140	7,0±4,6 (4) 33,0±8,0 (5)	<0,001	9,8±4,0 (5) 77,0±5,0	<0,001	5×10^{-4}	21,5±3,7 (6) 17,3±2,5 (6)	>0,5
MT-4 (10-amino-β-perhydroacridine)	50	0 (4) 77,7±0,4 (5)	<0,001	8,3±3,0 (5) 11,5±7,7 (6)	>0,5	5×10^{-4}	30,0±0,9 (6) 20,9±0,5 (6)	<0,001
MT-5 (10-isopropylamino-α-perhydro-acridine)	25	2,4±1,5 (6) 8,0±2,8 (5)	>0,5	4,2±3,2 (4) 34,8±8,5 (6)	<0,001	—	—	—
MT-6(10-isopropylamino-β-perhydro-acridine)	60	0 (4) 15,5±7,7 (7)	>0,5	0 (3) 35,3±3,7 (3)	<0,001	—	—	—
SOG-3 [N,N-dimethyl-α-(p-chlorophenoxy)-β-alanine 2-isopropylhydrazine]	153	11,6±3,8 (6) 30,0±10,7 (5)	>0,5	34,0±5,8 (6) 66,0±5,7 (7)	<0,01	—	—	—
SOG-18 [imidazole-4(5)-carboxylic acid 2-isopropylhydrazide]	286	33,7±7,2(5) 84,9±6,6 (5)	<0,01	53,0±3,9 (5) 74,4±5,4 (5)	<0,02	—	—	—
NG-4 (2-methyl-2-benzoylbenzhydrazide)	273	24,0±2,4 (5) 4,8±9,8 (4)	<0,05	57,0±3,8 (4) 71,5±4,2 (4)	<0,05	—	—	—

Note: 1) Compound injected intraperitoneally in experiments in vitro, except NG-4 which was given by mouth; 2) number of experiments shown in parentheses.

TABLE 2. Comparison of Effect of Hydrazine and Aminoperhydroacridine Derivatives on Serotonin Breakdown by Rat and Mouse Brain Homogenates in Experiments in Vivo and in Vitro

Compound	Dose (mg/kg)	Inhibition of serotonin breakdown by brain homogenates (%) in vivo		P	Dose (moles)	Inhibition of serotonin breakdown by brain homogenates (%) in vitro		P
		rat	mouse			rat	mouse	
Nialamide [Isonicotinic acid hydrazide N-benzyl(β-propionamide)]	30	51,0±5,0 (6)	91,4±6,7 (5)	<0,002	—	—	—	—
MG-3 (10-amino-α-perhydroacridine)	21	51,6±9,2 (6)	0 (5)	<0,001	5×10^{-3}	45,0±5,7 (5)	16,0±7,1 (5)	<0,02
NG-4 (2-methyl-2-benzoyl-benzhydrazide)	273	60,0±4,7 (10)	31,8±5,4 (5)	<0,001	—	—	—	—
SOG-5 (4,6-diphenylpyrimid-ine-2-carboxylic acid 2-isopropylhydrazide)	205	74,7±3,0 (4)	100±0 (5)	<0,001	—	—	—	—
SOG-18 [imidazole-4(5)-carb-oxylic acid 2-isopropyl-hydrazide]	286	53,0±3,9 (5)	0 (4)	<0,001	5×10^{-4} $2,5\times10^{-4}$	22,2±1,6 (5) 57,0±8,7 (5)	8,8±2,6 (5) 27,2±2,4 (5)	<0,001 <0,02

Note: Compound injected intraperitoneally 18 h before decapitation in experiments in vivo; 2) number of experiments given in parentheses.

EXPERIMENTAL RESULTS AND DISCUSSION

The compounds differed in their action on serotonin oxidation and in the different organs. For example the compounds NG-4, SOG-3, and SOG-18,* 2 and 18 h after administration, blocked serotonin breakdown by rat brain homogenates to a greater degree. The compounds SOG-7, MT-4, MT-5, and MT-6 inhibited serotonin inactivation by rat liver homogenates only (Table 1).

Species differences in the blocking action of some of the compounds on the enzyme also were found. For example, compounds MT-3, SOG-18, and NG-4 clearly inhibited serotonin oxidation by rat brain homogenates but had a much smaller influence on the breakdown of serotonin by mouse brain homogenates. The compounds SOG-5 and Nialamide, on the other hand, inhibited serotonin oxidation by mouse brain homogenates to a greater degree than its oxidation by rat brain homogenates (Table 2).

To determine whether the difference between the specific action of the tested compounds on the organs are connected with their ability to penetrate into the brain, the blocking effect of the compounds showing the greatest organ-specificity (SOG-7 and MT-4) were compared in experiments in vivo and in vitro. In vitro, SOG-7 and MT-4 were found to inhibit serotonin breakdown by both rats liver and brain homogenates to about the same degree (Table 1).

The possibility thus cannot be ruled out that the absence of a blocking action of compounds SOG-7 and MT-4 in vivo on brain MAO can be attributed to their inability to penetrate into the brain.

The species-selectivity of action of MAO inhibitors in vivo may be due to differences in the sensitivity of MAO from different species of animals to the blocking agents. This hypothesis was confirmed by further experiments. In particular, the effect of compounds MT-3 and SOG-18 on the serotonin breakdown by rat and mouse brain homogenates was compared in experiments in vivo and in vitro. The results showed that in vitro, just as in vivo, MT-3 and SOG-18 had a more marked inhibitory action on the inactivation of serotonin by rat brain homogenates than by mouse brain homogenates (Table 2).

Recalling similar data for the sensitivity of rat MAO to blocking agents [1, 2], it can be concluded that the compounds of the greatest practical interest are those with a marked inhibitory action on MAO in this species of experimental animal.

LITERATURE CITED

1. V. Z. Gorkin, L. V. Tat'yanenko, D. M. Krasnokutskaya, et al., Biokhimiya, No. 3, 510 (1967).
2. L. A. Romanova, Selective Inhibition of the Activity of Mitochondrial Amine Oxidases by Some Tricyclic Compounds and Other Monoamine Oxidase Inhibitors. Author's Abstract of Candidate's Dissertation, Moscow (1970).
3. Z. P. Khavronina and A. P. Gilev, Izv. Sibirsk. Otdel. Akad. Nauk SSSR, No. 10 (2), 128 (1968).
4. R. A. Khaunina, in: Antidepressants and the Treatment of Depressive States [in Russian], Leningrad (1966), p. 11.
5. M. Ozaki, H. Weissbach, A. Ozaki, et al., J. Med. Pharm. Chem., 2, 591 (1960).
6. P. Zeller, A. Pletscher, K. F. Gey, et al., Ann. N. Y. Acad. Sci., 80, 555 (1959).

*The chemical names of the compounds are given in Tables 1 and 2.