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ACTION OF PYRAZIDOLE ON EFFECTS OF SEROTONIN AND PHENYLETHYLAMINE

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The antidepressant pyrazidole differs from other known antidepressants in the spectrum of its psychopharmacologic activity [1].

The special features of pharmacologic activity of pyrazidole are determined primarily by its different effects on different brain monoamines. Biochemical studies have shown that pyrazidole inhibits oxidative deamination of serotonin but has virtually no effect on deamination of phenylethylamine (PEA) in the brain [1, 2]. The central serotonin-potentiating action of pyrazidole was manifested as potentiation of the convulsant activity of 5-hydroxytryptophan (5-HTP) [1].

In this paper new data are given in the antiserotonin action of pyrazidole and its action on the effects of PEA.

EXPERIMENTAL METHOD

The effect of pyrazidole on central serotoninergic structures was studied on mice by the use of 5-HTP by the method in [3]. Pyrazidole and, for comparison, imipramine were given internally in different doses 60 min before intraperitoneal injection of 5-HTP in a dose of 300 mg/kg. The number of head twitches of each mouse was determined in the course of 1 min 25 min after injection of 5-HTP. In a separate series of experiments the rectal temperature was measured 30 min after injection of 5-HTP, against the background of pyrazidole and imipramine.

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TABLE 1. Effect of Pyrazidole and Imipramine on the Hypothermic Action of 5-HTP in Mice (M ± m)

Preparation	Dose, mg/kg (internally)	Number of mice	Number of head twitches per mouse
Distilled water	—	80	6,7±0,3
Pyrazidole	10	80	8,5±0,49 †
	25	70	6,0±0,54
	50	70	3,0±0,81 ‡
Imipramine	10	30	5,6±0,46*
	25	50	4,6±0,63†
	50	40	3,8±0,72 ‡

*P < 0.05.
†P < 0.002.
‡P < 0.001.

TABLE 2. Effect of Pyrazidole and Imipramine on Head Twitching Induced by 5-HTP (300 mg/kg, intraperitoneally) in Mice (M ± m)

Preparation	Dose, mg/kg (internally)	Number of mice	Rectal temperature of mice receiving 5-HTP, °C
Distilled water	—	12	34,3±0,49*
Pyrazidole	10	6	36,9±0,35*
	25	6	37,4±0,63*
Imipramine	10	6	37,1±0,46*

*P < 0.002.

The peripheral antiserotonin action of pyrazidole was studied in experiments *in vitro* on the isolated rat uterine cornu (serotonin was added in a concentration of 1×10^{-8} g/ml) and *in vivo* by determining the decrease in serotonin edema of the rat limb (pyrazidole was injected intraperitoneally in doses of 25 and 50 mg/kg 30 min before subplantar injection of 5 μg serotonin).

Interaction with PEA was studied by methods described previously [4]. The effect of pyrazidole on the toxicity of PEA was investigated in groups of mice 3 h after injection of PEA. The mice were placed 10 at a time in metal boxes measuring 25 × 15 × 10 cm. Pyrazidole was given internally in different doses 60 min before intraperitoneal injection of PEA in doses of 25, 50, 75, and 100 mg/kg. To study its effects on the locomotor action of PEA, pyrazidole was given internally in a dose of 50 mg/kg 60 min before intraperitoneal injection of PEA in doses of 25, 50, and 100 mg/kg. Motor activity of the mice was measured on an "Animex" apparatus between 0-10 and 20-30 min after injection of PEA. For statistical analysis of the results Student's t test was used. The standard error of the arithmetic mean was determined at the P = 0.05 level.

EXPERIMENTAL RESULTS

Data on the effect of pyrazidole on the action of 5-HTP are given in Tables 1 and 2. As Table 1 shows, pyrazidole in a dose of 50 mg/kg, like imipramine, reduced the number of head twitches caused by 5-HTP. Although pyrazidole in a dose of 50 mg/kg did not inhibit the pinna reflex (head twitching in response to stimulation of the external auditory meatus with a hair), estimation of the decrease in the number of twitches induced by it as an antiserotonin effect was made difficult by the fact that pyrazidole potentiated the tremor and excitation due to 5-HTP. Imipramine potentiated these effects of 5-HTP by a lesser degree. In a dose of 10 mg/kg pyrazidole also intensified head twitching induced by 5-HTP. A stronger serotonin-positive effect of pyrazidole was observed after injection of 5-HTP in a subthreshold dose of 50 mg/kg (intraperitoneally), as reported previously [1].

The hypothermic effect of 5-HTP was reduced by pyrazidole, just as by imipramine (Table 2).

The antiserotonin action of pyrazidole was well marked in relation to the peripheral effects of serotonin: Serotonin contraction of the isolated rat uterine cornu and serotonin edema of the rat limb were reduced. In experiments *in vitro* on the isolated rat uterine cornu pyrazidole in concentrations of 2×10^{-7} to 2×10^{-6} g/ml reduced the action of serotonin by half, and in a concentration of 1×10^{-6} to 5×10^{-6} g/ml it abolished it completely. In these same concentrations pyrazidole did not affect spasm of the uterine cornu evoked by acetylcholine, confirming the specific antiserotonin action of the drug.

In doses of 25 and 50 mg/kg (intraperitoneally) pyrazidole, injected 30 min before subplantar injection of serotonin (5 μg), reduced serotonin edema of the limb. For instance, the weight of the limb into which serotonin was injected was increased by 46% compared with the weight of the limb into which the same volume of isotonic NaCl solution was injected,

TABLE 3. Effect of Pyrazidole on Mortality in Mice (in %) after Administration of PEA (M ± m)

Preparation	Dose mg/kg (internally)	Dose of PEA (intraperitoneally), mg/kg			
		25	50	70	100
Distilled water	—	0 ($n=10$)	26±8.3 ($n=30$)	56±20 ($n=30$)	66±8.3 ($n=30$)
Pyrazidole	10	0 ($n=10$)	23±8.8 ($n=30$)	50±16 ($n=30$)	80±16.7 ($n=20$)
	25	0 ($n=10$)	53±25 ($n=30$)	60±12.5 ($n=30$)	80±17.6 ($n=20$)
	50	10 ($n=10$)	73±4.1* ($n=30$)	76±4.2 ($n=30$)	80±17.6 ($n=20$)

*P < 0.05.

TABLE 4. Effect of Pyrazidole on Locomotor Action of PEA in Mice (M ± m)

Preparation	PEA dose (I.P.), mg/kg	Number of mice	Mean number of trips (per group of three mice) at undermentioned times after PEA injection	
			0-10 min	20-30 min
Distilled water	0	6	403±22	214±12
	25	12	318±74	135±23
	50	12	298±26	155±27
	100	18	490±61	630±70
Pyrazidole (50 mg/kg, internally)	25	12	217±15	70±18*
	50	24	332±29	199±22
	100	24	279±19†	689±42

*P < 0.02.
†P < 0.002.

but after preliminary injection of pyrazidole the weight of the limb into which serotonin was injected was increased by only 19% (dose of pyrazidole 25 mg/kg) and by 13% (dose 50 mg/kg.

Data on the effect of pyrazidole in the action of PEA are given in Tables 3 and 4. They show no clear potentiation of the toxicity of PEA by pyrazidole. PEA increased motor activity in a dose of 100 mg/kg but had virtually no effect on it in doses of 25 and 50 mg/kg. In a dose of 50 mg/kg (internally) pyrazidole did not potentiate the locomotor effect of PEA but, on the contrary, reduced it a little (Table 4).

The absence of any effect of pyrazidole on the central effects of PEA, shown by this investigation, whereas at the same time, it has the marked antireserpine and 5-HTP-potentiating actions established previously [1], is evidence that pyrazidole acts predominantly on activity of type A monoamine oxidase (MOA).

The serotonin-positive activity of pyrazidole can also be linked with the MAO (A)-inhibiting effect, whereas the serotonin-negative activity can probably be linked with the blocking action of the drug on postsynaptic serotonin receptors. The presence of these opposite effects of pyrazidole may be reflected in the particular features of its psychopharmacologic spectrum.

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