EFFECT OF ALKYLAMIDES OF IMIDAZOLE- AND PYRAZOLEDICARBOXYLIC ACIDS ON WATER AND MINERAL METABOLISM

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Alkylamides of imidazole- and pyrazoledicarboxylic acids (ethimizole and ethipyrole) increase sodium excretion in the urine and also cause a negligible increase in potassium excretion.

It was shown previously that alkylamides of imidazole- and pyrazoledicarboxylic acids have a marked central action, stimulate respiration, stimulate the hypothalamus–pituitary–adrenal cortex system, and inhibit water diuresis [1, 7-10].

In the investigation described below the action of these substances on water diuresis and excretion of electrolytes was studied in the case of ethimizole (dimethyldiamide of 4,5-imidazoledicarboxylic acid) and ethipyrole (dimethyldiamide of 3,4-pyrazoledicarboxylic acid).

EXPERIMENTAL METHOD

Experiments were carried out on intact, adrenalectomized, and hypophysectomized male rats weighing 140-200 g, which received water, warmed to 30°C, in a dose of 5% of the body weight through a gastric tube. Simultaneously with the water load, the test drugs were injected intraperitoneally. Control rats received intraperitoneal injections of physiological saline in the same volumes. Urine was collected in hourly samples for 4 h. The sodium and potassium concentrations in the urine were determined by flame photometry [4, 11] using the PPF-UNIIZ photometer. Changes in diuresis were expressed as percentages of the volume of water given. The adrenals were removed under ether anesthesia through a paravertebral incision. The animals were used in the experiment 5-6 days after the operation. Hypophysectomy on the rats was performed under ether anesthesia through a parapharyngeal approach [6]. Completeness of removal of the pituitary glands was verified after the experiments by examination of the sella turcica under a binocular loupe. Results obtained on incompletely hypophysectomized animals were disregarded. These rats were used in the experiment 10-12 days after hypophysectomy. The test drugs (ethimizole and ethipyrole) were given in doses of 5-40 mg/kg. The numerical results were treated by statistical methods [2].

RESULTS AND DISCUSSION

Under the influence of ethimizole (20 mg/kg) and ethipyrole (40 mg/kg) water diuresis was inhibited during the first 2 h. The total volume of water excreted during 4 h did not differ significantly from the control following administration of ethimizole, and was slightly reduced after injection of ethipyrole. The excretion of sodium in the urine was increased significantly following the administration of these compounds, but the excretion of potassium showed a negligible increase. Ethimizole increased sodium excretion more strongly than ethipyrole. This effect of the compounds was also observed after their administration in

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TABLE 1. Effect of Ethimizole and Ethipyrole on Water Diuresis of Rats and on Excretion of Sodium and Potassium in Urine (M ± m)

Group of animals	No. of animals	Compound injected	Doses (in mg/kg)	Diuresis (in % of water load)					Excretion of electrolytes during 4 h (in mg)	
				1 h	2 h	3 h	4 h	total in 4 h	sodium	potassium
Intact	170	Control		46,0±3,9	43,3±3,4	11,2±0,6	6,5±0,6	107,3±2,6	2,26±0,2	6,9±0,7
	9	Ethimizole	10	28,4±3,2	45,4±4,1	32,6±2,8	10,0±1,3	116,4±6,8	5,56±0,5	7,5±1,0
	32	"	20	13,1±1,3	21,1±3,5	37,5±1,6	20,7±3,2	92,4±4,6	12,35±1,6	9,5±0,5
	12	Ethipyrole	20	28,7±3,0	37,5±3,1	30,4±2,8	12,3±1,0	108,9±4,3	4,17±0,6	7,0±0,9
	30	"	40	10,1±1,2	24,9±3,2	20,8±1,1	18,5±1,3	74,3±4,0	5,91±0,5	7,3±0,7
Hypophysectomized	25	Control		6,5±0,9	37,8±3,3	37,7±4,3	9,1±1,0	91,1±6,4	0,5±0,1	5,0±0,5
	15	Ethimizole	20	3,8±0,6	2,3±0,4	4,8±0,5	20,0±1,3	30,9±3,8	5,21±0,8	4,2±0,4
	9	Ethipyrole	40	0	5,4±0,5	10,2±1,3	6,0±0,6	21,6±1,9	2,1±0,3	4,1±0,6
Adrenalectomized	28	Control		5,0±0,6	13,6±1,5	7,8±0,9	7,9±0,6	34,3±2,2	2,33±0,3	6,6±1,1
	13	Ethimizole	10	5,0±1,0	9,4±0,8	3,5±0,5	6,5±0,6	24,4±1,9	4,87±0,4	6,5±0,7
	16	Ethipyrole	20	4,2±0,9	5,7±0,7	4,0±0,8	2,6±0,6	16,5±1,7	2,39±0,3	4,8±0,6

small doses (5-10 mg/kg), before any delay in diuresis was observed. Under the influence of ethinizole in doses having no significant effect on water diuresis, the sodium excretion was increased by 2.5 times, and the Na/K ratio was more than doubled. Following administration of this compound in a dose of 20 mg/kg, sodium excretion was increased by more than 5 times, and the Na/K ratio by more than 4 times. The effects of these compounds in inhibiting diuresis and increasing sodium excretion in the urine persisted for 6 days if frequent, large doses were given. However, under the influence of small doses of these compounds (especially of ethimizole), an increase in the excretion of sodium was observed without any significant effect on water diuresis or potassium excretion.

The next series of experiments was carried out on hypophysectomized rats. No polyuria was observed in these animals, in agreement with observations [3, 5]. Meanwhile, the sodium concentration in the urine of the hypophysectomized rats was considerably lower than in the intact animals. No significant change took place in the potassium excretion in the urine. Despite inhibition of diuresis, following injection of the test compounds a marked increase was observed in sodium excretion (Table 1). These results indicate that inhibition of diuresis and stimulation of sodium excretion in the urine by these compounds can take place even in the absence of pituitary hormones. Administration of these compounds to adrenalectomized animals produced a definite inhibition of water diuresis (Table 1). The sodium excretion in the urine over a period of 4 h was increased in the experiments with ethimizole (Na/K ratio doubled), while in the experiments with ethipyrole no significant changes were observed by comparison with adrenalectomized animals not receiving the compounds. It follows from the results obtained on adrenalectomized rats that the adrenals do not play a decisive role in the observed effects of these two compounds.

It must be emphasized that irrespective of the changes in water diuresis produced by these compounds, the Na/K ratio rose. The Na/K ratio was increased with an increase in the dose of the compounds. The change in the Na/K ratio taking place under these circumstances was on account of sodium because the excretion of potassium in the urine in the various series of experiments showed no significant difference from that in the control animals (Table 1).

The results of these experiments show that alkylamides of imidazole- and pyrazoledicarboxylic acids, besides producing a central analeptic action and activation of hypothalamus–pituitary–adrenal cortex system, also exert a direct effect on renal mechanisms of water and mineral metabolism. These two compounds may be of interest as potential stimulators of sodium excretion.

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