MECHANISM OF THE LIPID-MOBILIZING ACTION OF ETHIMIZOLE

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The effect of ethimizole on the mobilization of fatty acids and the role of hormones of the pituitary—adrenal system in the lipolytic effect of ethimizole were studied in experiments on rats. The lipid-mobilizing action of ethimizole was well marked in intact, hypophysectomized, and adrenalectomized rats. The effect of the drug disappeared in animals after simultaneous extirpation of the pituitary and adrenals but was restored when these animals were given hydrocortisone. It is concluded that ethimizole has a direct action on the mobilization of fatty acids and that corticosteroids play a permissive role in the lipid-mobilizing effect of ethimizole.

KEY WORDS: *ethimizole; free fatty acids; corticosteroids.*

Analogs of the methylxanthines and, in particular, ethimizole, cause mobilization of the lipid and carbohydrate reserves of intact and hypophysectomized rats [8]. The lipid-mobilizing effect of ethimizole is connected with activation of secretion of ACTH [6, 7, 9], which has a marked lipolytic action [16, 17], and also with the ability of the methylxanthines and their analogs to inhibit activity of cyclic AMP phosphodiesterase [10]. Ethimizole can also activate adenyl cyclase [5].

The object of this investigation was to study the role of hormones of the pituitary—adrenal system in the mechanism of the lipid-mobilizing action of ethimizole.

EXPERIMENTAL METHOD

Experiments were carried out on 396 male rats weighing 180-200 g kept on a standard diet. Hypophysectomy and adrenalectomy (singly and together) were performed on the rats. The animals were used in the experiments 3-4 days after the operations. Activity of the pituitary—adrenal system was judged from the blood level of 11-hydroxycorticosteroids (11-HCS) [12]. The level of free fatty acids (FFA) [18] and glucose [2] was determined in the blood plasma. Ethimizole and diaphylline (euphylline) were given in doses of 20 mg/kg, adrenalin and noradrenalin in a dose of 1 mg/kg, and ACTH in a dose of 1 unit per rat (all intraperitoneally). The control rats received an injection of the same volume of physiological saline. The animals were decapitated 60 min after injection of the substances and their blood was collected. The results were subjected to statistical analysis [1].

EXPERIMENTAL RESULTS AND DISCUSSION

The plasma 11-HCS and FFA levels 1 h after injection of ethimizole into intact rats were considerably raised (Table 1). Hypophysectomy and adrenalectomy on the control rats lowered their blood 11-HCS level but did not change the FFA or glucose concentrations. The blood FFA concentration 1 h after injection of ethimizole into hypophysectomized rats increased, although by a much lesser degree than in the intact animals. This may perhaps be explained by the incidental effect of ACTH, the secretion of which is increased in intact rats by ethimizole [6-9]. However, since the elevation of the FFA level under the influence

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TABLE 1. Effect of Ethimizole, Diaphylline, and Catecholamines on 11-HCS, FFA, and Glucose Concentrations in Rat Blood Plasma (M ± m)

Animals	Substance	11-HCS, μg %	FFA, meq/liter	Glucose, mg %
Intact	Control	13,9±0,4	334,7±8,2	137,2±3,5
	ACTH	24,4±0,8†	851,0±19,4†	130,0±3,6
	Adrenalin	30,1±1,0†	809,7±23,2†	234,0±7,1†
	Noradrenalin	24,4±0,7†	740,3±22,7†	109,1±6,2*
	Ethimizole	32,8±1,3†	970,0±26,1†	153,1±3,2*
	Diaphylline	18,4±0,8*	682,5±25,5†	146,1±6,3
Hypophysectomized	Control	3,4±0,4	345,3±10,3	126,2±5,1
	ACTH	19,8±0,9†	605,9±23,0†	130,2±2,6
	Adrenalin	4,8±0,6	277,9±21,6*	191,0±8,0†
	Noradrenalin	5,5±0,5	476,8±18,4†	135,6±4,3
	Ethimizole	4,6±0,4	565,0±22,2†	198,1±8,2†
	Diaphylline	5,1±0,5	574,2±22,5†	130,5±4,7
Adrenalectomized	Control	5,1±0,4	344,3±9,4	129,4±3,0
	ACTH	4,0±0,3	462,3±16,3†	119,3±3,2
	Adrenalin	3,9±0,5	446,1±17,0†	191,4±7,4†
	Noradrenalin	4,2±0,4	586,3±20,5†	122,2±3,4
	Ethimizole	5,7±0,5	560,0±20,8†	135,0±3,6
	Diaphylline	5,5±0,6	505,4±19,2†	124,5±4,5
Hypophysectomized and adrenalectomized	Control	4,7±0,4	322,5±8,4	129,0±3,0
	ACTH	4,2±0,5	760,2±21,6†	123,0±3,6
	Adrenalin	4,9±0,5	342,8±18,2	158,8±4,9†
	Noradrenalin	5,2±0,6	282,2±16,3*	117,3±7,2*
	Ethimizole	5,0±0,5	346,0±19,1	135,0±3,6
	Diaphylline	4,6±0,4	332,6±20,4	120,4±3,3
Hypophysectomized and adrenalectomized, treated with hydrocortisone (5 mg/kg daily for 4 days)	Control	4,8±0,5	486,6±17,7	138,5±4,2
	ACTH	5,0±0,6	746,2±23,1†	91,0±9,2†
	Adrenalin	5,8±0,5	730,0±24,6†	227,8±9,0†
	Noradrenalin	4,8±0,4	691,3±21,8†	129,1±4,3
	Ethimizole	5,1±0,5	772,1±23,5†	155,9±7,0*
	Diaphylline	5,4±0,5	752,6±29,8†	131,7±6,6

*P < 0.05.

†P < 0.01 compared with corresponding control.

of ethimizole was still manifested in the hypophysectomized animals, this suggests the presence of a peripheral component in the mechanism of the lipid-mobilizing action of this substance.

The hyperlipemic response to injection of ethimizole was considerably weakened in the adrenalectomized rats also. This may have been due both to deficiency of glucocorticoids and to "exhaustion" of the adipose tissue as a result of the increased ACTH secretion in these animals. The role of this last factor is confirmed by the fact that the lipid-mobilizing action of ACTH is weaker in adrenalectomized rats than in intact or hypophysectomized rats.

After simultaneous hypophysectomy and adrenalectomy no increase in the blood FFA concentration was observed in response to ethimizole. However, this fact cannot be regarded as proof of the absence of any direct lipid-mobilizing effect of ethimizole on adipose tissue, for against the background of injection of hydrocortisone (5 mg/kg daily for 4 days) into such animals the increase in the blood FFA concentration after injection of ethimizole was almost equal in magnitude to that in intact rats.

These results suggest that for the direct lipid-mobilizing action of ethimizole on adipose tissue to be manifested, adrenocortical hormones, which evidently play a permissive role in lipolytic processes [3, 4], must be present in the blood stream.

Experiments with adrenalin and noradrenalin which, like ethimizole, stimulate ACTH secretion [11, 13] and activate adenyl cyclase, and also with diaphylline, which inhibits phosphodiesterase, thus causing accumulation of cyclic AMP in both cases, were carried out for comparison. Analysis of the results showed that the mechanism of the lipolytic action of ethimizole is similar to that of catecholamines and methylxanthines. In every case the

corticosteroids were evidently able to give rise to a manifest lipid-mobilizing action by activating adenyl cyclase, by inhibiting phosphodiesterase, or by potentiating the effect of cyclic AMP on the protein kinase of adipose tissue [14].

With regard to carbohydrate metabolism, in rats of all groups adrenalin gave a hyperglycemic effect, the degree of which was smallest in adrenalectomized and hypophysectomized animals. This result agrees with data in the literature [15]. The hyperglycemic action of ethimizole, which was much weaker, could be based on the same mechanisms as that of adrenalin.

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