EFFECT OF SIGETIN ON TRIGLYCERIDE AND CHOLESTEROL LEVELS IN RAT BLOOD AND LIVER

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Sigetin, a dihydrostilbestrol analog but without estrogenic action, lowers the cholesterol concentration in intact rats and also after administration of dexamethasone. Sigetin prevents the elevation of the blood triglyceride level observed in rats under the influence both of diethylstilbestrol and of other agents, notably ethanol and dexamethasone.

KEY WORDS: hyperlipidemia; triglycerides; cholesterol; diethylstilbestrol.

Many investigators have shown that estrogens have a hypocholesteremic and antiatherosclerotic action under experimental conditions [5, 7, 9]. However, their clinical use to lower the raised blood cholesterol and β-lipoprotein level is restricted because of their side effects, including a marked increase in the blood triglyceride concentration and the danger of thrombosis [10]. The study of the effect of estrogen derivatives deprived of their estrogenic effect but, because of their structural similarity, still preserving certain metabolic aspects of the action of estrogens, is therefore of great interest. One such substance is the Soviet compound [6] sigetin (the dipotassium salt of p,p-disulfomeso-3,4-diphenylhexane). In experiments on rabbits, sigetin had a hypocholesteremic action [4], but its effect on the triglyceride concentration has not been studied.

The object of this investigation was to study the action of sigetin on the triglyceride and cholesterol concentrations in the blood and liver of intact rats and also in animals with hyperlipidemia, induced by dexamethasone and ethanol, and during the combined administration of sigetin and diethylstilbestrol.

EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing 180-200 g. The animals received a standard diet (concentrates, vegetables, water). The substances to be studied were administered in the following doses over a period of 9 days: sigetin, 100 mg/kg intraperitoneally twice a day; diethylstilbestrol, 1 mg/kg intramuscularly, once a day; dexamethasone (dexason, from Galenika, Yugoslavia), 0.1 mg/kg intramuscularly, once a day. Ethanol was given for 3 days in a dose of 6 g/kg body weight daily as a 50% solution (via gastric tube). In control experiments the solvent was given in equal volumes. The animals were deprived of food for 18 h before sacrifice. The concentrations of total cholesterol [8] and of triglycerides [11] in the blood serum and liver were determined. The results were subjected to statistical analysis [1].

EXPERIMENTAL RESULTS

As Table 1 shows, administration of sigetin to intact rats caused a decrease in the serum cholesterol level. The triglyceride levels in the blood and liver were unchanged in these animals. However, under conditions of hypertriglyceridemia, developing in the animals after the influence of ethanol, administration of sigetin prevented the rise in the blood triglyceride concentration and caused a definite tendency for their concentration in the liver to fall (Table 1). The hypolipidemic action of sigetin also was exhibited after administration of the glucocorticoids dexamethasone, as shown by a decrease in the blood cholesterol concentration and a tendency for the elevated triglyceride level to fall.

To study the efficacy of sigetin as a hypolipidemic agent, its action was compared with that of diethylstilbestrol. As Table 1 shows, under the influence of the estrogen the serum cholesterol level of the rats distinctly fell, whereas at the same time there was a marked increase in the triglyceride concentration. Combined administration of sigetin and diethylstilbestrol led to a marked decrease in the rise of the serum triglyceride level. No difference was found in the cholesterol concentrations in the blood and liver of these animals.

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TABLE 1. Lipid Concentration in Blood Serum and Liver of Rats (M ± m)

Substance administered	Cholesterol		Triglycerides	
	serum, mg %	liver, mg/g	serum, mg %	liver, mg/g
Physiological saline (22)	85,8±3,1	2,4±0,11	63.8±4.5	13,4±0.4
Sigetin (15)	64,1±1,14*	2,6±0,15	64,1±4,2	13,1±0,6
Physiological saline (13)	84,0±5,7	2,9±0,23	68,8±8.6	13.4±1.0
Dexamethasone (15)	106±2,7*	2,6±0,14	113,0±12.2*	14.5±0,7
Dexamethasone + sigetin (15)	75,0±1,6	2,8±0,15	104,0±8,6	15.6±0,65
Physiological saline (10)	—	—	63,0±4,23	13,3±0,72
Ethanol (10)	—	—	116,0±9,8 *	20.0±1,5*
Ethanol + sigetin (10)	—	—	57,6±4.3	16.6±1,3
Physiological saline (15)	85,3±2,3	2,5±0.13	67.8±6.7	14.2±0.21
Diethylstilbestrol (15)	20,0±2,3*	2,7±0.18	128±6,3*	9.6±0,54* (10→9)
Diethylstilbestrol + sigetin (15)	21,4±2,3	2,8±0,14	98,9±6.0*	12,7±0.64

Note. Number of animals given in parentheses; asterisk denotes values differing significantly ($P < 0.005$) from corresponding control.

The results show that sigetin has a less marked hypocholesteremic action than diethylstilbestrol. However, unlike the latter, administration of sigetin not only does not cause an increase in the blood triglyceride concentration, but it actually prevents such an increase caused by the estrogen. Sigetin, incidentally, has the property of inhibiting estrogen-sensitive receptors and thus preventing manifestation of some of the typical effects of estrogens: their action on the ovaries, uterus, and secretion of hormones by the pituitary [2,3]. The results of the present experiments show that sigetin prevents elevation of the blood triglyceride level observed in rats under the influence either of diethylstilbestrol or of other agents, such as ethanol and, to a certain degree, dexamethasone. It can therefore be concluded that its hypolipidemic action is not connected with ability to inhibit estrogen-sensitive receptors. This conclusion is also confirmed by data on the hypocholesteremic action of sigetin in intact rats or rats treated with dexamethasone. This property of sigetin, of lowering the triglyceride level, must be taken into account when its clinical use is contemplated.

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