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THE EFFECT OF EPINEPHRINE ON SERUM LIPOPROTEINS

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ABSTRACT

Epinephrine injection has been shown to produce a two to ten fold increase of the higher Sf classes of serum lipoproteins in the rabbit. The previously observed elevation of serum lipids was confirmed.

The hyperlipoproteinemia following epinephrine injection appears at about the same time as in certain conditions of stress.

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Introduction

There is considerable evidence implicating the sympatho-adrenal system in lipid metabolism. Hemi-sympathectomy has been shown to alter the fat content of the denervated tissue,[1,2,3] and the importance of epinephrine in the mobilization of fat to the liver has been demonstrated.[4] Kaplan and Gort have shown that the injection of epinephrine into dogs produced an elevation of serum phospholipid, total cholesterol, and esterified fatty acids within 24 hours.[5] The lipids returned to pre-injection levels within 48 hours after a single injection, but the hyperlipemia could be maintained for as long as 8 days by the daily injection of epinephrine.

Dury has recently published studies on the effects of epinephrine on lipid partition in the rabbit.[6] He reports elevated levels of certain serum lipoproteins following epinephrine projection and suggests that epinephrine may stimulate the mobilization of triglyceride from fat depots and their transport in the form of macromolecules of the blood.

The serum lipoproteins represent an important part of lipid metabolism and have been studied extensively, particularly in their relationship to atherosclerosis.[7] Also, elevated serum lipoprotein levels have been shown following total-body x-irradiation,[8] local irradiation,[9] burn shock,[10] and extensive bleeding.[11] The hyperlipoproteinemia shown in these stress conditions could be due in part to an increased level of circulating epinephrine.

Because of the proven effect of epinephrine on lipid metabolism and because of the observed elevation of serum lipoproteins in certain stress conditions, an investigation of the effect of epinephrine on serum lipoproteins was undertaken.

Materials and Methods

New Zealand White rabbits of 2 to 4 kg body weight were used. Epinephrine in peanut oil (Parke Davis, 2 mg/ml) was injected (0.5 mg/kilo) intramuscularly every 6 hours for 1 day (i.e. 0, 6, 12, 18, 24 hours) in the first series of animals, and 0.3 mg/kg per day for 6 consecutive days and 0.6 mg/kg for another 7 days in the second series. Equal volumes of peanut oil were used for control injections. Heparin (Lederle-American Cyanamid Co. 100 mg/ml) was given to two animals in a single dose of 10 mg intravenously. Blood samples were taken just prior to the injection of epinephrine for that day. Serum lipoproteins were analyzed according to the procedure described by deLalla and Gofman[12] and Hewitt and Hayes.[11] The serum lipids were extracted with methanol ethyl ether, the lipids separated chromatographically on a silicic acid column, and the fractions analyzed by infrared spectrophotometry.[13]

Results

Effects of Epinephrine Administration on Serum Lipoprotein Concentration

There is no immediate change in lipoprotein levels following the injection of epinephrine in oil, but at about 18 hours the Sf 30–100 and 100–400 classes begin to increase in the serum and reach a maximum at about 2 days in the first series of animals, and at 6 to 14 days in the second series. The general effect of epinephrine injection is to increase the higher Sf classes (Sf 30–400) of lipoproteins, as much as 2 to 10 fold, while the lower Sf classes (Sf 0–30) show little difference from the controls. Elevated concentration of these lower Sf classes was observed in both control and treated animals, presumably owing to some other factor than epinephrine--probably the peanut oil. The results are shown in Figs. 1 and 2.

Effects of Epinephrine in Serum Lipids

The serum lipids of four rabbits of Series 2 were determined by infrared analysis[13] before and 6 days after the beginning of treatment. The largest increases were found in the triglyceride and phospholipid fractions. Free cholesterol and free fatty acids were also significantly elevated. The results are shown in Table I.

The Effect of Heparin in Epinephrine-Induced Lipemia

Heparin clears the alimentary lipemia[14, 15] as well as radiation-induced lipemia,[8] and in both cases it appears to involve an alteration of lipoprotein distribution. The blood chemistry shows a decrease of triglyceride accompanied by a release of free fatty acids, suggesting a lypolytic action of heparin.[16, 17] It was of interest to know if heparin had the same effect on adrenalin-induced lipemia. Ten mg of heparin was given intravenously to two rabbits at the fourteenth day of epinephrine-induced lipemia. Blood samples were taken just prior to and at 40 minutes after the heparin injection. Table II indicates that heparin administration decreased the higher Sf classes of lipoproteins and increased the lower Sf classes.

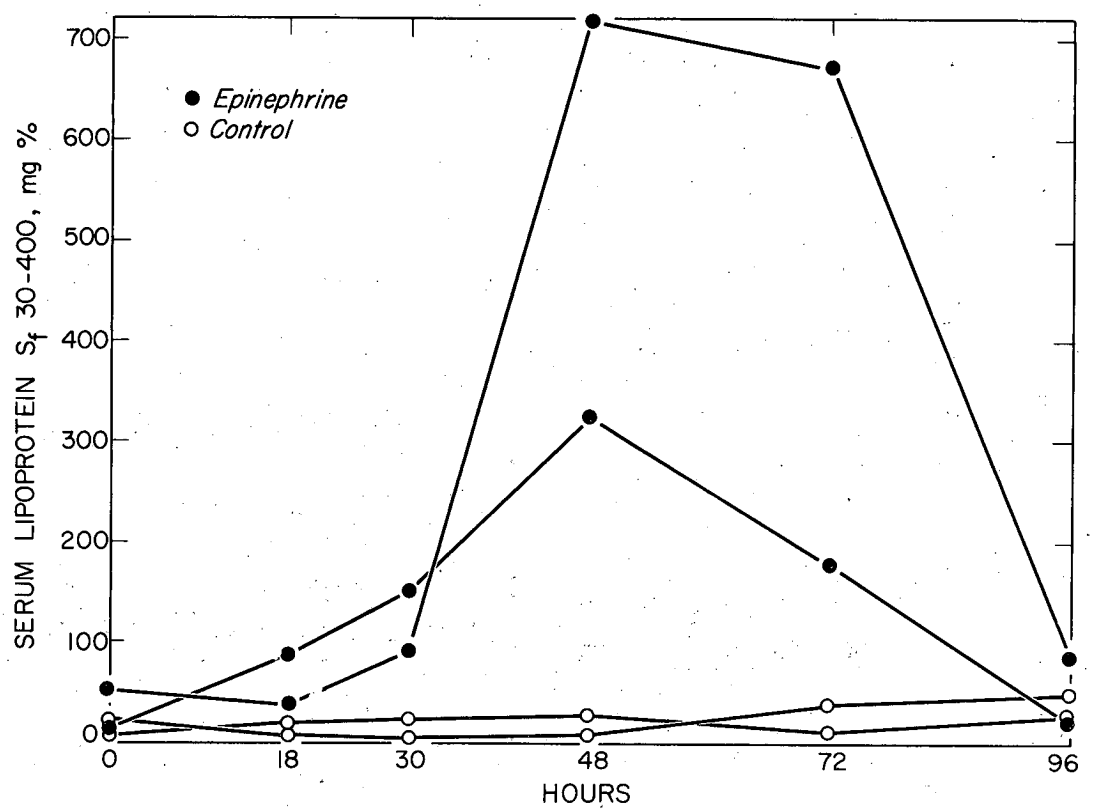

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Fig. 1. Effect of epinephrine on the higher Sf classes of serum lipoproteins. Epinephrine (0.5 mg/kilo) given every 6 hours for 1 day.

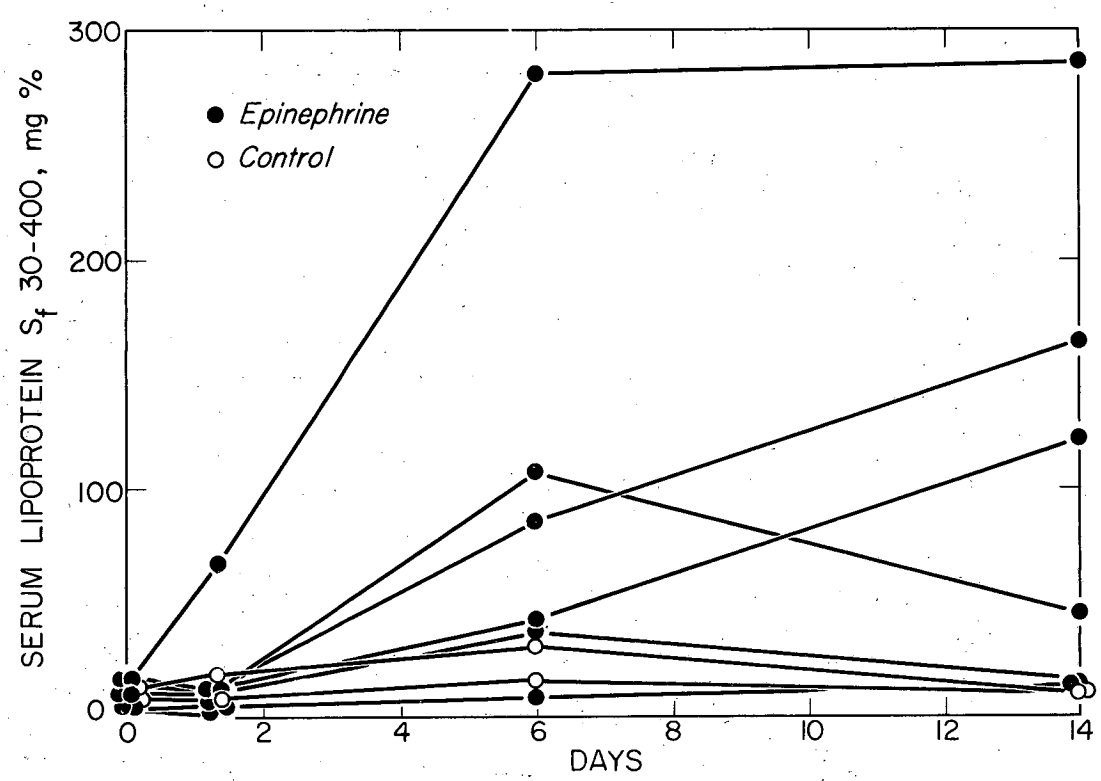

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Fig. 2. Effect of epinephrine on the higher Sf classes of lipoproteins. Epinephrine (0.3 g/kilo) daily for 6 days followed by epinephrine (0.6 mg/kilo) daily for 7 days.

Table I

Serum lipid changes after epinephrine injection

Animal	Day	Triglyceride (mg%)	Fatty Acid (mg%)	Phospho lipid (mg%)	Unesterified cholesterol (mg%)
22 (control)	0	55.4	19.2	127	42.9
	6	55.5	19.0	69.5	28.6
24	0	50.5	20.7	69.0	15.8
	6	97.0	32.2	179.2	35.8
25	0	57.6	20.0	79.4	34.4
	6	225.4	85.1	193.2	86.7
26	0	48.2	20.3	66.1	25.6
	6	82.3	31.9	96.0	32.3

Table II

The action of heparin (10 mg IV) on the epinephrine-induced hyperlipoproteinemia

	Lipoproteins (Sf)					
Rabbit	5-15 mg %	15-30 mg %	30-100 mg %	100-400 mg %	T.G. mg %	F.A. mg %
21 pre	10	5	57	44		
post	40	5	5	5		
25 pre	45	23	105	180	637	43
post	91	32	52	20	263	126

This supports the previously suggested theory of transformation of lipoproteins of higher flotation rates to lipoproteins of lower Sf rates.[7,14] Table II also shows that there is a decrease of triglyceride and simultaneously an increase of free fatty acids, as previously noted in other types of lipemia.

Discussion

The observations described above confirm the report by Dury that certain serum lipoproteins increase in concentration following the injection of epinephrine.[6] The rabbits receiving 2 mg/kilo epinephrine over a 1-day period gave a more pronounced response than those receiving 0.3 or 0.6 mg/kilo daily (Series 2). In every case the hyperlipoproteinemia was not apparent until 18 hours or more after the commencement of treatment. This delay in the appearance of large amounts of lipoprotein in the blood is similar to that seen in stress conditions,[10,11] and is in contrast to the very early elevation of blood sugar following epinephrine injection or irradiation.[18]

It seems possible that the level of circulating epinephrine plays an important role in the production of hyperlipoproteinemia under conditions of stress. This work also suggests that elevated levels of circulating epinephrine should be considered as a possible cause of chronically elevated serum lipids and lipoproteins.

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