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Plasma Triglyceride Production in Man. Effect of Noradrenaline Infusion. *

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Fatty acid transport in the blood occurs mainly in two ways: as free or non-esterified fatty acids (FFA), which are bound to the serum albumin, and as esterified fatty acids, mainly in the form of triglycerides (TG) in the very low density lipoproteins (VLDL) *Robinson* 1970. Esterified fatty acids in blood plasma are also present in cholesterol-esters and phospholipids, but these fractions will not be discussed here.

FFA enter the bloodstream from adipose tissue located at various sites, e.g. subcutaneous and omental. This process is generally referred to as FFA mobilization. The uptake of FFA occurs in skelektal muscle, myocardium (*Carlson, Kaijser and Lassers* 1970) and the liver (*Boberg, Carlson, Freyschuss, Lassers* and *Wahlqvist* 1972).

It is well known that mobilization of FFA from adipose tissue is stimulated by noradrenaline. Under the influence of noradrenaline a considerable increase occurs both in concentration and turnover rate of plasma FFA (*Carlson, Boberg* and *Högstedt* 1965).

In the present comunication, values for plasma TG production in subjects with normal plasma TG concentrations and in patients with hypertriglyceridemia are given. Furthermore, evidence is provided that plasma FFA are the main precursors of plasma TG, and finally, what occurs if plasma FFA turnover rate is increased with an infusion of noradrenaline.

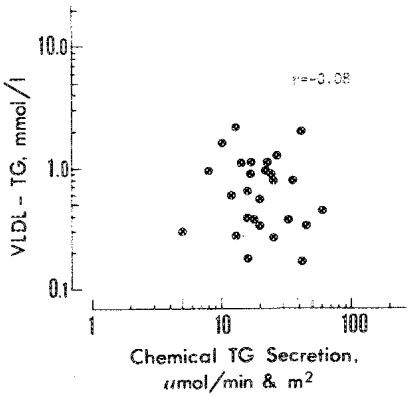

Fig. 1 The relationship between triglyceride (TG) production and plasma very low density lipoprotein (VLDL) TG concentration in male subjects with normotriglyceridemia. r is coefficient of correlation. Logarithmic values are used because of skewness in distribution.

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Table 1. Data for plasma free fatty acid (FFA) and triglyceride (TG) transport during noradrenaline infusion

Table 1 Data for plasma free fatty acid (FFA) and triglyceride (TG) transport during noradrenaline infusion

Subject no	Age yrs	Body weight kg	Body surface area m^2	Plasma concentration TG µmol/ml	CHOL mg/100 ml	Plasma FFA µmol/min/m^2 turnover rate	splanchnic uptake*	splanchnic mobilization	Plasma TG production** µmol/min/m^2	Splanchnic blood-plasma flow % of plasma volume per minute	Noradrenaline infusion rate µg/min/kg b.w.
1	57	72	1.82	0.90	227	478 ± 29	300 ± 76	208 ± 76	42	17	0.10
2	24	66	1.84	0.88	–	347 ± 6	166 ± 18	74 ± 10	21	18	0.10
3	58	84	2.00	1.80	224	450 ± 5	229 ± 8	129 ± 13	31	22	0.10
4	40	74	1.89	1.07	148	257 ± 9	234 ± 9	132 ± 10	28	32	0.03
Controls** (logarithmic value)	41 ± 2	74 ± 2	1.89 ± 0.004	1.23 (1.090 ± 0.044)	203±8	282 ± 18	192 ± 21	110 ± 16	19 (1.282 ± 0.054)	29 ± 2	0

* maximum value (see *Havel et al.* 1970)
** chemical secretion method (see *Boberg et al.* 1972). Mean value ± standard error of the mean.
*** 21 subjects with normal lipoprotein patterns (see *Boberg et al.* 1972). Mean value ± standard error of the mean.

The methods used in the present studies have been described in detail (*Boberg, Carlson* and *Freyschuss* 1972). Since blood analyzed for plasma TG concentration was simultaneously sampled from an artery and from the hepatic vein, and splanchnic blood plasma flow was determined at the same time, net production of plasma TG across the splanchnic area could be measured.

Plasma TG Production in Man

Plasma TG production varies between 5 and 61 µmol per minute and m^2 body surface area (b s a) in subjects with normotriglyceridemia (Figure 1), and the mean value is 19, µmol per minute and m^2 b s a (Table 1). No correlation exists between plasma TG production and plasma VLDL - TG concentration ($r = -0.08$ (Figure 1).

In patients with hypertriglyceridemia plasma TG production varies between 6 and 184 µmol per minute and m^2 b s a and a significantly positive correlation ($r = 0.65$) is found between this production rate and plasma VLDL – TG concentration (Figure 2). The mean value of plasma TG production in these patients was 28, µmol per minute and m^2 b s a which is not significantly different from the mean value for normotriglyceridemics. However, four patients with hypertriglyceridemia had a plasma TG production value above the range of the normals.

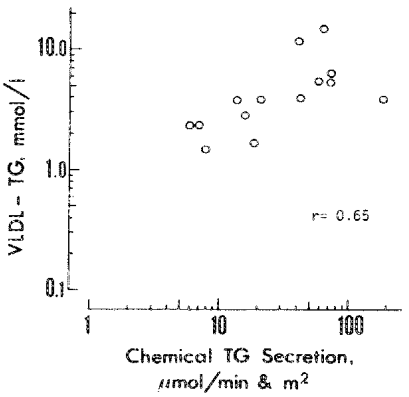

Fig. 2 The relationship between plasma triglyceride (TG) production and plasma very low density lipoprotein (VLDL) TG concentration in male subjects with hypertriglyceridemia. r is coefficient of correlation. Logarithmic values are used because of skewness in distribution

Plasma TG Production and Splanchnic Uptake of Plasma FFA

In subjects with normal plasma TG concentration there is an increased plasma TG production with increased uptake of plasma FFA. This relationship is significantly linear and follows the equation y=x: (0.09 ± 0.02) + 5.3 obtained by regression analysis (y = plasma TG production and x = splanchnic FFA

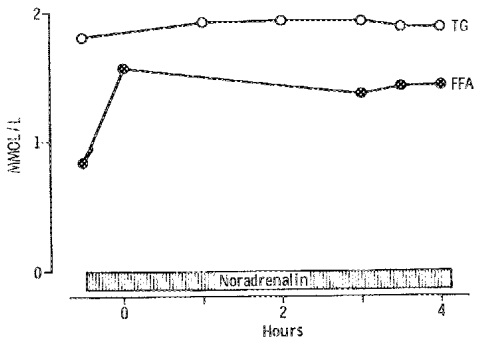

Fig. 3 Effect of a constant infusion of noradrenaline (0.1 μg/min/kg body weight) on plasma free fatty acids (FFA) and triglycerides (TG).

uptake). Some patients with hypertriglyceridemia fall inside this relationship while 4 out of 14 fall outside the limits of 99 per cent confidence. This latter circumstance indicates that precursors other than plasma FFA contribute to plasma TG production (*Boberg et al.* 1972).

Effect of Noradrenaline Infusion on Splanchnic FFA and TG Transport

In four apparently healthy volunteer subjects a noradrenaline infusion was given for 4.5 hours (see Fig. 3) in order to increase plasma FFA turnover rate. During the last hour, blood was sampled for measurements of plasma FFA and TG transport across the splanchnic area as described previously (*Boberg, Carlson and Freyschuss* 1972). The results of the investigations are given in Table 1.

When noradrenaline was infused at the rate of 0.1 μg per minute and kg body weight (Table 1, cases 1-3), plasma FFA concentration and turnover rate were increased significantly ($p < 0.05$) to values about 70 and 50 per cent respectively above those found in control subjects. Also the mean value for splanchnic uptake and mobilization of FFA was increased, but only slightly, and the increase was not significant.

The plasma TG concentration did not change during the noradrenaline infusion. Plasma TG production however was increased on the average about 30 per cent but this increase was not significant.

Total plasma FFA turnover rate increased relatively more than the splanchnic FFA transport parameters and plasma TG production, apparently because splanchnic blood plasma flow decreased during the noradrenaline infusion.

Concluding Remarks

Plasma TG production was essentially in the same range for normo- and hypertriglyceridemia, who had a considerably increased value. This means that increased values of plasma VLDL-TG concentrations in patients with hypertriglyceridemia are mainly due to impaired removal mechanisms of plasma VLDL-TG, since most of these patients get increased plasma VLDL-TG concentrations in spite of plasma TG production rates in the same range as normotriglyceridemic subjects. In about half of the patients, however, the plasma TG productions were in the upper part of the normal range and seemed to have contributed to the hypertriglyceridemia in these patients.

At rest after 14 hours fasting about 60 per cent of total FFA turnover rate is taken up by the liver. This amount is equal to 200 μEq per minute and m^2 b s a. About one third of this uptake is used for ketone body formation (*Carlson, Freyschuss, Kjellberg and Östmann* 1967, *Havel, Kane, Balasse, Segel and Basso* 1970) and one third goes to plasma TG production (*Boberg, Carlson and Freyschuss* 1972). The last third may very well go to complete oxidation, since mean oxygen consumption for the liver is about 40 ml per minute and m^2 b s a in man (*Greenway and Stark* 1971).

The infusion of noradrenaline into dogs has earlier been shown to increase plasma concentration and turnover of FFA (*Carlson, Liljedahl and Wirsen* 1965). In the same studies plasma TG concentrations also increased, but not until after 8 hours infusion. The present results demonstrate that noradrenaline increases plasma FFA concentration and turnover rate also in man. However, the expected effects of noradrenaline in increasing splanchnic fatty acid transport are partly counteracted by the decreased splanchnic blood plasma flow during noradrenaline infusion.

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Discussion

N. Zöllner: Two questions for Dr. Nikkilä: first, am I correct to assume that during the experiment triglyceride levels remained constant and secondly, did you separate the various lipoproteins and measure triglyceride levels in these individually?

E. Nikkilä: Yes, you have to be in a steady state and try to have constant triglyceride concentrations during the study. Cases where this could not be achieved were discarded. And secondly, no, we did not isolate lipoproteins. All the data presented are obtained from total plasma triglyceride concentrations.

G. Schlierf: I was very impressed by the large amount of studies you have done. However, I would like to mention that the production rates and other data you give are actually obtained in a state which the human subjects usually are not in, namely a prolonged fast. Usually, when people are eating high fat diets the concentrations of triglycerides are changing very much during the day, or when they are eating high carbohydrate diets the triglycerides vary considerably during the night. Obviously, the metabolic state changes continuously and turnover studies such as yours do not give true "life" information.

E. Nikkilä: I agree with this though I do not think that we have better methods today for study of the turnover in these patients. Steady state has to be reached though this does not reflect the actual situation in life.

G. Mancini: Prof. Nikkilä, do you have any data on the turnover of plasma free fatty acids in your untreated diabetics and, if you do, have you correlated them with the plasma triglyceride concentrations?

E. Nikkilä: No, we do not have such data.

J. Bobert: I think something has to be said about the methodology for measuring plasma TG production. Prof. Nikkilä said that we did not measure the production from the intestine and that is certainly true. However, we can define what we are measuring, namely the net production of plasma TG across the splanchnic area. Our values for plasma TG production are actually 5 times higher than his values, which indicates that if we don't measure the contribution from the intestine, I suppose that he probably does not either.

I have one question for Dr. Nikkilä: was there any difference in age between group I and II since we have seen when we give injections of exogenous triglycerides behaving as a tracer dose of plasm triglycerides, we see that people in older ages have a slower fractional removal rate than younger people.

E. Nikkilä: These people were of identical age. So, I think that age did not influence these differences.

Current Views on Cholesterol Metabolism

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An altered cholesterol metabolism in man is clinically associated with several disease groups. Of these, the development of atherosclerosis via hypercholesterolemia and the role of bile acids, catabolites of cholesterol, in various gastroenterological disorders, such as gall-stone disease, malabsorption and diarrhoea, are the most important (cf. *Miettinen* 1972 b). Although great progress has been made during recent years in our understanding of cholesterol and bile acid metabolism, especially in the field of gastroenterology, the mechanisms of hypercholesterolemia are still basically unknown. This is partly due to insufficient knowledge of the factors influencing cholesterol metabolism and the interactions between the blood cholesterol level, cholesterol synthesis and catabolism, and tissue cholesterol. In the present paper some recent developments in the field of human cholesterol metabolism will be presented.

Factors Normally Influencing Cholesterol Metabolism

Intestinal degradation. Cholesterol is eliminated from the human body by the faecal route as bile acids and neutral sterols (cholesterol, coprostanol and coprostanone). Thus, in the steady state, sterol balance, i.e., the difference between dietary cholesterol, on the one hand, and faecal acidic and neutral sterols of cholesterol origin, on the other, is equal to cholesterol sythesis. However, during intestinal passage a variable amount of cholesterol, and dietary plant sterols as well, is degraded to undetectable derivatives at least on a formula diet (*Grundy, Ahrens and Salen 1968).* This loss of sterols has not been detected on a solid food diet or a formula diet containing cellulose and lactose (*Denbesten, Connor, Kent* and *Lin* 1970, *Kottke* and *Ravi Subbiah* 1971). In our series of more than 200 patients (low-cholesterol, quite low-lactose, solid food diet) recovery of orally administered