Short-term effect of nicotinic acid on plasma level and turnover of free fatty acids in sheep and man

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ABSTRACT The effects of nicotinic acid on plasma free fatty acid levels and turnover and on plasma glycerol levels were studied in the first few hours after administration to man and the sheep. In both species a fall in all parameters studied was followed by a rise above basal level, interpreted as due to an increase in lipolysis above resting level. The significance of the findings is discussed.

SUPPLEMENTARY KEY WORDS glycerol · rebound effect

NICOTINIC ACID has been shown to depress plasma levels of free fatty acids (FFA) in man and the dog (1) and in the rat (2).

The nicotinic acid-induced depression of plasma FFA level can be interpreted as due to inhibition of lipolysis of adipose tissue triglycerides, since both basal and noradrenaline-stimulated release of FFA from fat in vitro are also inhibited by nicotinic acid (3). In the studies of Carlson and Orö (1) plasma FFA rose above the baseline level in man after an oral dose of nicotinic acid; the rise was not inhibited by further, but smaller, doses. The rebound rise of plasma FFA after nicotinic acid administration has also been noted in rats and dogs (4). The following study reports the effect of nicotinic acid in man and the sheep on plasma FFA levels and on turnover, and on plasma levels of nicotinic acid and glycerol.

MATERIALS AND METHODS

Female sheep (*Ovis aries* L), 1–1.5 yr old and weighing 30–48 kg, were used in the nonfasted, conscious state. In four animals an arteriovenous anastomosis had been made between the external jugular vein and common carotid artery. The animals were allowed to recover for several weeks after the operation. In this way we could easily obtain arterial blood from the distended venous channel without unduly disturbing the animal. In six other animals we took samples via a polythene catheter in the external jugular vein. At the end of the "baseline" sampling period 500 mg of sterile sodium nicotinate was given intravenously and sampling was continued for periods of up to 4.5 hr. Albumin-bound palmitic acid-9,10-^{3}H (500 mc/mmole) was infused into the opposite external jugular vein at a constant rate of approximately 4 μc/min.

Tritium-labeled palmitic acid for these studies was obtained from the New England Nuclear Corp. and purified before use by thin-layer chromatography on Silica Gel G (E. Merck, A.G.). 70–80% of the original radioactivity was recovered in the fatty acid area and eluted for use.

Studies in man were carried out on middle-aged male patients admitted for investigation of peripheral vascular disease. None of the patients was overtly diabetic. The patients were investigated after an overnight fast and prepared by the insertion of a catheter into the brachial artery for sampling purposes. Albumin-bound palmitic acid-9,10-^{3}H was infused into an antecubital vein on the opposite arm at about 1.5 μc/min. After baseline sampling at 15-min intervals for 1 hr, 500 mg of nicotinic acid was given orally.

Plasma FFA were measured by the Trout, Estes, and Friedberg (5) modification of the Dole (6) method. Plasma FFA radioactivity was measured after separation of the fatty acids by thin-layer chromatography (7)

Abbreviation: FFA, free fatty acids.

and radioactivity was measured in a Packard Tri-Carb scintillation counter. All tubes were corrected for quenching by means of an internal standard. FFA turnover was calculated by the formula of Havel, Carlson, Ekelund, and Holmgren (8), which assumes that palmitate turnover is representative of the turnover of all fatty acids.

Plasma nicotinic acid was determined by the method of Carlson (9), plasma glycerol, by the method of Laurell and Tibbling (10).

RESULTS

Sheep

The results of the two studies in sheep are presented in Table 1. Table 2 shows the arterial plasma values of nicotinic acid at intervals after the intravenous dose. Fig. 1 shows the pattern of plasma FFA response in the study using arterial blood.

In both types of investigation a pronounced fall of the plasma FFA level and turnover was seen shortly after the intravenous administration of nicotinic acid. The plasma glycerol level showed a fall which appeared to parallel that seen in the FFA parameters. The low point of the plasma FFA occurred 40–50 min after injection of the nicotinic acid and was followed by a rise above baseline levels (for plasma FFA concentration, glycerol level, and FFA turnover) from about 80 min after injection. Levels tended to fluctuate after 80 min, with a return to basal levels after about 160 min in some animals.

The depression of FFA level and turnover is significant ($P < 0.001$) and the maximal elevation of FFA levels and turnover is also significant ($P < 0.02$). Plasma nicotinic acid levels were recorded during the above phases; the rise of FFA and glycerol occurred when plasma nicotinic acid levels had declined to about 1 mg/liter.

The similarity in patterns of response in the two series of animals studied here indicates that the changes in level and total turnover of plasma FFA are reflected fairly in venous blood samples, although the generally higher total turnover values after arterial sampling may indicate that the drainage area of the vein has some influence on results.

Patients

The studies on patients given an oral dose of 500 mg of nicotinic acid gave the results shown in Table 1 and Fig. 2. Although the time scale is different, the same general trend as in the sheep was observed. The apparent absence of a rebound in FFA level in one of the subjects is due to the early termination of the study for technical reasons.

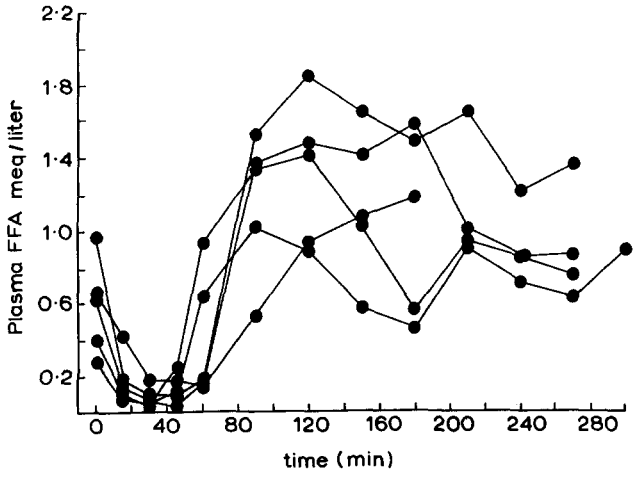

FIG. 1. Arterial plasma FFA levels after intravenous injection of 500 mg of nicotinic acid in the sheep. Nicotinic acid given at zero time.

The plasma FFA levels, which reached their minima between 40 and 120 min, were significantly lower than the mean basal levels ($P < 0.01$). The maximum level of plasma FFA was significantly greater than the basal levels ($P < 0.01$). The changes in FFA total turnover paralleled those in the FFA level, the lowest turnover rate being significantly lower than the basal ($P < 0.01$) and the turnover rate during the rebound phase significantly higher than basal ($0.01 < P < 0.02$).

DISCUSSION

The depression of plasma FFA level and reduction of total FFA turnover produced by nicotinic acid in the sheep is in keeping with the action of this substance in other species. The elevation of total FFA turnover during the rebound phase indicates that the elevation of plasma FFA level is due to increased mobilization of fatty acids, presumably from adipose tissue triglycerides, and is not the result of decreased utilization. Support for the view that the rising plasma FFA level in the rebound phase was due to increased lipolysis is provided by the increasing plasma glycerol level, since glycerol that results from complete hydrolysis of triglycerides is not available for reesterification within adipose tissue.

The actual fate of the mobilized fatty acids cannot be deduced from our investigations, but it may be presumed that FFA recycles to some extent into triglycerides of adipose and other tissues (11, 12); increased respiratory utilization at the expense of glucose is also possible. It might also be expected that increased FFA flux in the absence of increased metabolic demand would result in increased synthesis of triglyceride-rich very low density lipoproteins. The sheep, however, shows little incorpora-

TABLE 1 EFFECT OF NICOTINIC ACID ON PLASMA LEVELS AND TURNOVER OF FREE FATTY ACIDS AND PLASMA GLYCEROL

	Sheep		Man
	Venous Blood	Arterial Blood	Arterial Blood
Mean basal plasma FFA (*meq/liter*)	0.65 ± 0.04 (30)*	0.62 ± 0.06 (22)	0.64 ± 0.03 (23)
Mean basal FFA turnover (*μmoles/min*)	451 ± 23 (24)	804 ± 97 (14)	549 ± 46 (16)
Mean basal plasma glycerol (*mmole/liter*)	—	0.071 ± 0.007 (15)	0.166 ± 0.008 (16)
Minimum plasma FFA level (after nicotinic acid) (*meq/liter*)	0.11 ± 0.002 (6)	0.08 ± 0.02 (5)	0.19 ± 0.03 (5)
Corresponding plasma FFA turnover (*μmoles/min*)	90 ± 3 (6)	199 ± 103 (4)	151 ± 10 (5)
Corresponding plasma glycerol (*mmole/liter*)	—	0.031 ± 0.003 (3)	0.095 ± 0.029 (4)
Corresponding plasma nicotinic acid level (*mg/liter*)	12.4 ± 1.62 (4)	8.4 ± 2.55 (5)	7.6 ± 2.91 (5)
Maximum plasma FFA level (after nicotinic acid) (*meq/liter*)	1.54 ± 0.11 (6)	1.41 ± 0.13 (5)	1.24 ± 0.25 (5)
Corresponding plasma FFA turnover (*μmoles/min*)	769 ± 104 (6)	1510 ± 291 (4)	763 ± 57 (3)
Corresponding plasma glycerol (*mmole/liter*)	—	0.180 ± 0.018 (5)	0.262 ± 0.019 (4)
Corresponding plasma nicotinic acid level (*mg/liter*)	1.0 ± 0.18 (4)	0.7 ± 0.10 (5)	1.12 ± 0.07 (5)

500 mg of nicotinic acid given to sheep intravenously and to man orally.
* Mean ± SEM (n).

TABLE 2 ARTERIAL PLASMA NICOTINIC ACID LEVELS IN SHEEP

Time	Plasma Nicotinic Acid
min	*mg/liter*
15	22.7 ± 3.68
30	10.2 ± 2.35
45	4.2 ± 1.25
60	2.1 ± 0.59
90	1.1 ± 0.14
120	0.6 ± 0.18
150	0.6 ± 0.06
180	0.5 ± 0.06
210	0.3 ± 0.23
240	0.3 ± 0.22
270	0.2 ± 0.19

500 mg of nicotinic acid was injected intravenously at zero time. Values are means ± SEM; n = 5 up to 180 min, 4 thereafter.

tion of ^{14}C-labeled palmitic acid into plasma triglycerides (13), and its total plasma triglyceride levels are low (13, 14) compared with man. Thus while the pattern of response of plasma FFA to administered nicotinic acid appears similar to other species reported, the fate of plasma FFA may be different among species (15).

The rebound of the plasma FFA after the low level has also been recorded for man, rat, and dog (1, 4). In investigating the mechanism of the rebound of plasma FFA level Pereira (4) showed that, at least in the rat, an intact pituitary–adrenal system was necessary for the phenomenon to occur and that it was not abolished by reserpinization of the rat. The possibility remains, however, that pituitary–adrenal factors might have a permis-

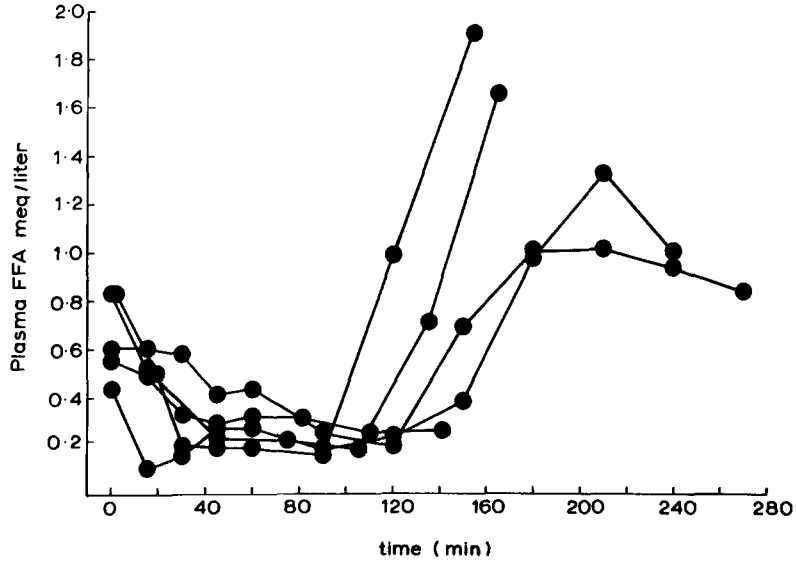

FIG. 2. Arterial plasma FFA levels after ingestion of 500 mg of nicotinic acid in man. Nicotinic acid given at zero time.

sive effect on lipolytic systems. Thus stimulation of lipolytic systems occurring after the effect of nicotinic acid has worn off may be ineffective in the absence of the pituitary–adrenal system; the definitive stimulus for lipolysis in the rebound phase remains to be identified.

The response is unlikely to be simply the result of lowering the plasma FFA since, as Pereira has shown, no rebound follows the FFA depression induced by pyridyl-3-acetic acid. A further possibility is that lipolysis is stimulated by an unknown metabolite of nicotinic acid, or, less likely, that low concentrations of nicotinic acid itself stimulate lipolysis.

Contributions to the observed effects of nicotinic acid on plasma FFA could also occur at other sites. Thus the stimulation of glycogenolysis in the liver by nicotinic acid, without a concomitant rise in the level of plasma glucose (16), implies an increased glucose flux which could be associated with increased uptake and reesterification of FFA in adipose tissue.

Detailed knowledge of the total effect of nicotinic acid on lipid economy awaits elucidation.

Our thanks are due to Dr. R. Laverty of the Wellcome Research Institute, Dunedin, for providing facilities for the determination of plasma glycerol and to Dr. S. P. Woodhouse for his valuable cooperation. Dr. W. A. A. G. Macbeth kindly performed the arteriovenous anastomoses. The technical assistance of Miss M. Craik and Mr. W. T. Poulsen is gratefully acknowledged.

This work was supported by the Medical Research Council of New Zealand.

Manuscript received 10 June 1968; accepted 3 October 1968.

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