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EFFECT OF PREVIOUS STARVATION ON THE RESPONSE OF PLASMA LIPIDS AND FREE FATTY ACIDS TO A FAT MEAL*

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Plasma free fatty acids (also variously referred to as nonesterified fatty acids and unesterified fatty acids) have assumed importance as a small but very rapidly metabolized component of serum lipids (1, 2). Their derivation from the fat of adipose tissue has been demonstrated and may represent an important form in which stored fat is mobilized, transported and made available for fuel during starvation (3).

The concentration of free fatty acids (FFA) in plasma increases during starvation (4), in the "metabolic" starvation of diabetic acidosis (5) and of hyperthyroidism (6). When an overnight fast is terminated by the administration of 50 to 100 g of carbohydrate, an abrupt fall in concentration of plasma FFA occurs within one-half hour and lasts for several hours, and a similar but less marked drop follows a protein meal (1, 2). On the other hand, following a fat meal of equal or greater caloric value, the FFA either do not change appreciably or rise much as they do during a similar period of fasting (2, 7).

The decrease in concentration of FFA appears to occur in response to an increase in carbohydrate utilization. The absence of such a drop in concentration after a fat meal would seem to indicate insensitivity of the FFA regulatory system to fat or merely the substitution of FFA derived from ingested fat for those derived from adipose fat (3). An alternative possibility is herein suggested, namely that relative inefficiency of fat metabolism in persons adapted to a high car-

bohydrate diet might account for the failure of a fat meal to cut off the FFA-mobilizing mechanism. Any nutritional or metabolic maneuvers aimed at increasing fat combustion might alter the response of plasma FFA to a fat meal.

The present study is concerned with the change in plasma lipids including FFA when a fat meal was administered at the end of a period of starvation lasting for several days.

MATERIALS AND METHODS

The subjects, who were in their twenties and were free of known disease, were 6 males, and 2 females. A third woman became ill from the effects of the first 24 hours of starvation and had to be dropped from the study. To 6 of the subjects a fat breakfast was given after an overnight fast, and again at the end of a period of starvation lasting from 2 to 7 days. During the starvation nothing but water was ingested. The subjects carried on their usual activities despite the discomforts of starvation.

The breakfast given to 5 of the 6 subjects receiving the fat meal consisted of 2 eggs, 28 g butter, and 60 ml heavy cream scrambled together. This meal supplies 60 g of fat, 12 g protein, and no carbohydrate. The sixth subject (B. B.) was given the same meal with the difference that the egg white was removed, thus eliminating the small amount of protein present in the breakfast.

In order to compare the effects of the fat breakfast with the effects of a carbohydrate meal, two additional male subjects were fed, after an overnight fast, 100 g of glucose dissolved in 400 ml of water flavored with lemon juice. The same amount of glucose was again administered after 3 days of starvation.

At intervals before and after the test meals and in some instances during the starvation, blood was drawn from an antecubital vein in a heparinized syringe, immediately centrifuged at room temperature, and the plasma separated from the cells. An aliquot for FFA determination was precipitated in the extraction mixture within one-half hour of the venipuncture.

FFA were determined by the Method of Dole (2), using a modified method of standardizing the alkali (8). Total fatty acids (9), total cholesterol (10) and lipid

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TABLE I
*Changes in plasma lipids following a fat meal given after an overnight fast (control)
 and terminating a period of several days' starvation*

Subject Sex		Time after Bk*	Cholesterol	Lip. P	Triglyceride fatty acids	FFA
		hrs	mg/100 ml	mg/100 ml	mEq/L	mEq/L
A. M. M	Control	Fasting	216	10.5	2.3	0.38
		3	202	10.4	7.9	0.47
		5	197	11.0	10.0	0.64
	Refeeding on 4th day of starvation	Fasting	219	9.9	5.5	1.40
		3	240	9.2	9.7	0.79
		5	213	11.3	6.7	0.63
	Repeat 1 wk later	Fasting	194	9.5	3.0	0.50
		3	218	11.0	6.0	0.40
		5	211	10.3	6.0	0.55
	Control	Fasting	202	9.2	3.4	0.38
		3	190	8.3	4.4	0.55
		5	193	9.7	5.0	0.75
B. B. M	Refeeding on 4th day of starvation	Fasting	250	10.0	5.8	2.63
		3	245	10.8	6.3	1.74
		5	243	10.7	6.1	1.79
	Control	Fasting	238	7.8	6.7	0.41
		3	257	8.3	6.6	0.48
		5	275	9.5	6.4	2.25
R. N. M	Refeeding on 8th day of starvation	Fasting	254	10.1	8.2	1.71
		3	254	10.1	8.2	1.71
		5	254	10.1	8.2	1.71
	Control	Fasting	238	7.8	6.7	0.41
		3	257	8.3	6.6	0.48
		5	275	9.5	6.4	2.25
S. H. M	Refeeding on 3rd day of starvation	Fasting	256	9.7	3.2	0.25
		3	253	11.3	5.3	0.42
		5	247	9.2	6.0	0.65
	Control	Fasting	239	9.7	4.5	2.01
		3	244	10.2	4.7	1.26
		5	235	10.3	3.1	1.28
J. G. F	Refeeding on 3rd day of starvation	Fasting	186	8.1	2.3	0.50
		3	193	8.5	4.6	0.62
		5	185	9.4	2.9	0.69
	Control	Fasting	182	7.2	3.2	0.96
		3	180	8.6	2.6	1.07
		5	189	8.9	2.9	1.18
M. D. F	Refeeding on 4th day of starvation	Fasting	205	9.7	1.7	0.45
		3	217	11.1	2.8	0.57
		5	214	10.9	2.7	0.57
	Control	Fasting	252	11.9	5.6	2.12
		3	250	13.9	6.3	1.25
		5	255	12.9	6.4	1.13

* Bk = breakfast containing 60 g of fat but no carbohydrate.

phosphorus (11) were determined on a chloroform-methanol extract. Triglyceride concentration was estimated by subtracting the fatty acids estimated to be combined with cholesterol and phospholipid from the total fatty acids. Blood glucose (12) was determined in the subjects receiving glucose.

RESULTS

Response to fat meal. The results are listed in Table I. Three and five hours following the control breakfast, the plasma FFA concentration increased in all six subjects, and triglyceride con-

centration increased in five of the six subjects. Plasma cholesterol and phospholipid concentrations did not change consistently.

In three subjects studied during the course of starvation, two of whom are represented in Figures 1 and 2, a rise in plasma FFA during the first day of starvation was indistinguishable from the changes after the fat meal. With continuation of starvation there was a definite but not consistent afternoon rise, with a drop occurring by the next morning. The overall trend was that of a progressive increase in plasma FFA concentration.

On the final morning of starvation, the FFA had increased in the plasma of all subjects from an initial average concentration of 0.39 mEq per L on the control morning to an average of 1.89 mEq per L (Tables I and II, Figures 1 and 2). The highest concentration of 2.7 mEq per L was achieved in the subject who had fasted a week (R. N.). An increase in cholesterol concentration occurred in the plasma of only three of the subjects, and in the concentration of triglycerides in five. The increases in triglyceride concentration were less than 5 mEq per L, and might in part represent FFA partially included in the chloroform-methanol extract.

The fat meal which terminated the fast produced an opposite effect on plasma FFA concentration from that of the control meal in five of the six subjects: in all but one female subject (J. G.), a sharp drop in concentration of FFA occurred three and five hours after the fat meal (Table I). The subject receiving no protein with his breakfast (B. B.) had as marked a drop as the others.

All uniformly reported restitution of energy and sense of well-being following the refeeding, with disappearance of weakness and fatigue which had become prominent during the starvation period. In one subject the fat breakfast was repeated one week following the termination of starvation (A. M.). The FFA response was intermediate between the control response and the post-starvation response.

Alimentary rise in triglyceride concentration was slightly lower following the starvation period than in the control period of five of the six subjects.

Response to oral glucose. Table II shows the slight fall in all lipid components and a marked fall in FFA when glucose was given after an overnight fast (control). After three days of starvation the high concentrations of FFA achieved by the fasting fell abruptly following the ingestion of glucose, reaching normal concentrations two and three hours after the glucose. Slight decrease in the concentration of all serum lipid frac-

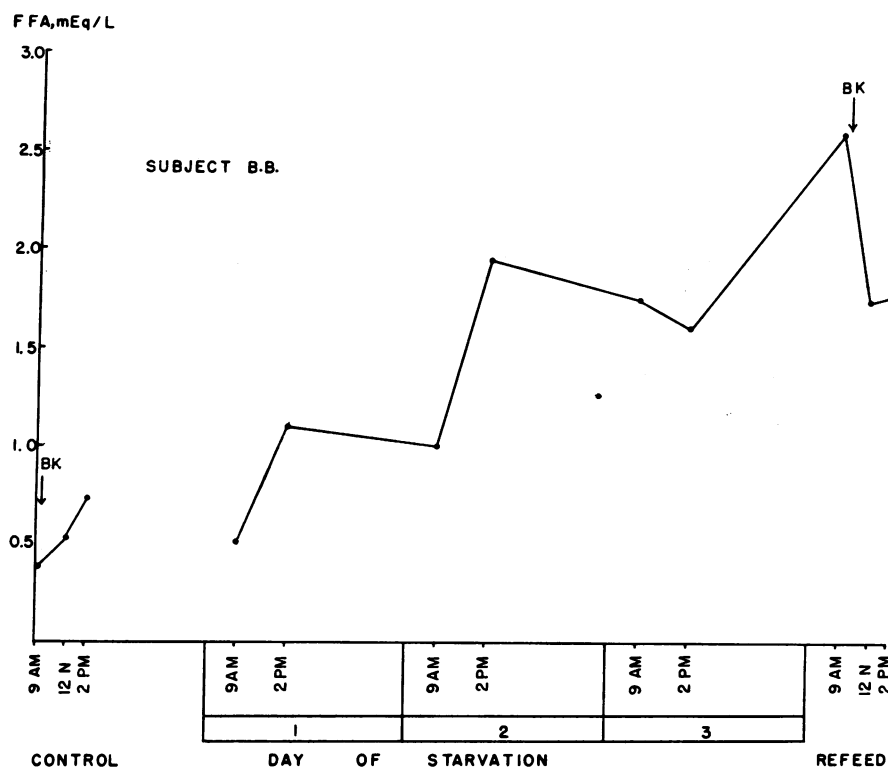


FIG. 1. SUBJECT B. B., PLASMA FREE FATTY ACIDS BEFORE AND AFTER A CONTROL FAT MEAL, DURING A THREE DAY PERIOD OF STARVATION, AND AFTER FEEDING A FAT MEAL AT THE CONCLUSION OF THE STARVATION PERIOD. FFA = free fatty acids; BK = breakfast containing 60 g of fat but no carbohydrate.

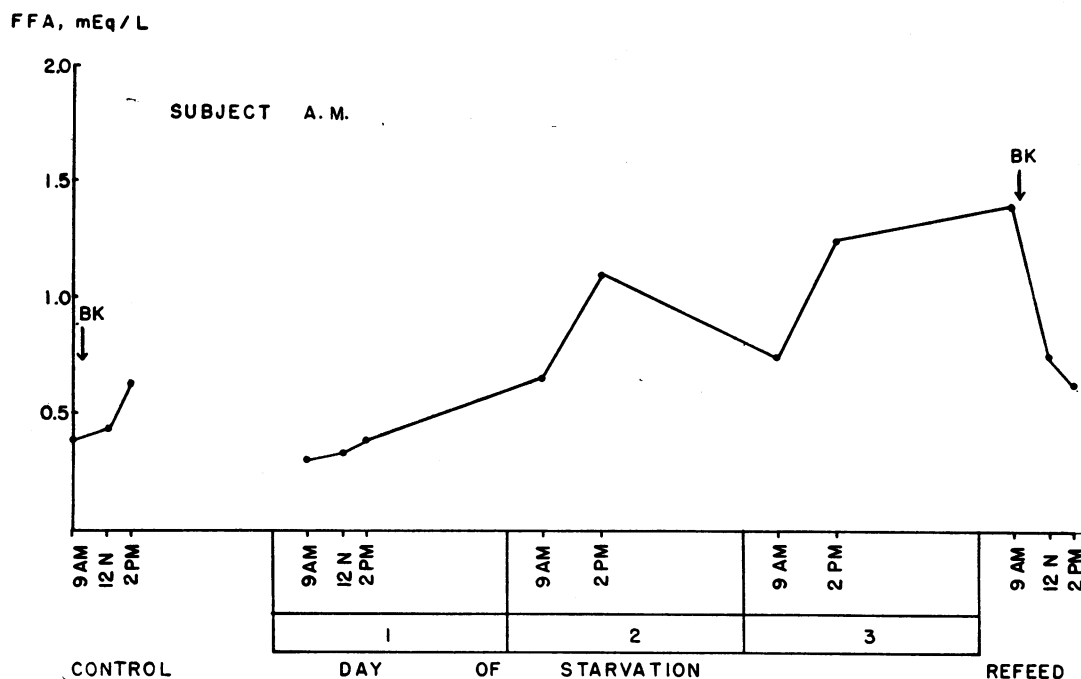


FIG. 2. SUBJECT A. M., PLASMA FREE FATTY ACIDS BEFORE AND AFTER A CONTROL FAT MEAL, DURING A THREE DAY PERIOD OF STARVATION, AND AFTER FEEDING A FAT MEAL AT THE CONCLUSION OF THE STARVATION PERIOD.

tions occurred in response to glucose. In contrast to the normal glucose tolerance curves of the control day, both subjects displayed markedly diabetic types of tolerance curves on the refeeding

day. Despite the profound response of FFA to glucose refeeding, the subjects did not experience a sense of well-being such as that reported by the subjects refed with the fat meal.

TABLE II
Changes in plasma lipids and blood sugar following 100 g oral glucose given after an overnight fast (control), and terminating a period of three days' starvation

Subject Sex		Time after glucose	Cholesterol	Lip. P	Triglyceride fatty acids	FFA	Blood sugar
		hrs	mg/100 ml	mg/100 ml	mEq/L	mEq/L	mg/100 ml
W. P. M	Control	Fasting	161	6.7	1.7	0.34	87
		1	156	6.5	1.9	0.21	106
		2	158	6.6	1.7	0.18	83
		3	150	6.1	1.4	0.18	83
		5				0.63	93
	Refeeding on 4th day of starvation	Fasting	180	8.0	3.7	0.94	66
		1	165	7.1	2.8	0.59	155
		2	165	7.2	3.2	0.34	157
		3	148	7.2	1.0	0.25	109
		5	169	7.5	1.7	0.64	59
	Control	Fasting	138	6.6	0.9	0.41	82
		1	129	6.3	1.2	0.17	121
		2	135	6.4	0.5	0.11	79
		3	129	5.5	0.6	0.11	74
		5	132	6.4	1.2	0.70	62
	Refeeding on 4th day of starvation	Fasting	177	7.9	10.7	2.91	52
		1	155	7.1	8.2	1.20	186
		2	156	7.0	7.1	0.49	212
		3	154	6.9	6.9	0.43	216
		5	161	6.8	6.9	0.99	110

DISCUSSION

The abrupt fall in concentration of plasma FFA when a two to seven day fast is terminated by feeding a fat meal is compatible with the hypothesis that fat metabolism becomes more efficient during a period of starvation. This drop is in sharp contrast to the lack of response or even rise in FFA concentration when a fat meal follows a fast of only a few hours or overnight. Evidence currently available supports the theory that a rise in plasma FFA concentration represents mobilization of fat from adipose tissue in response to a caloric deficit (3). Conversely, a decrease in FFA concentration signals caloric satisfaction from exogenous sources with concomitant cessation of delivery of FFA to plasma from adipose tissue. Prior to the present study, only maneuvers which either directly or indirectly increase carbohydrate combustion have been found to "cut off" the release of FFA (3). The failure of a fat meal to produce a fall in plasma FFA concentration under normal circumstances may very well mean that fat alone does not, under these circumstances, provide caloric satisfaction. Following the adaptive changes of starvation, a fat meal evidently does provide caloric satisfaction. The failure of one of the two women in the study to make this adaptation might stem from her sex, her tendency to obesity, or from the brevity of her period of starvation (two days). The decreased alimentary lipemia of all but one subject might be another manifestation of increased fat metabolism, although delayed gastric emptying and slow intestinal absorption cannot be ruled out.

The possible mechanisms whereby starvation increases the efficacy of fat as fuel are worthy of some consideration. Since a greater portion of administered fat is oxidized in briefly starved than in carbohydrate-fed animals (13), it stands to reason that after prolonged starvation, administered fat would be even more completely oxidized with a resultant increase in metabolic rate. If the FFA releasing mechanism responds in some way to energy balance rather than to some specific aspect of carbohydrate metabolism, the effect of refeeding a fat meal might cut off the mobilization of FFA from adipose tissue.

As an alternative explanation for the fall in FFA concentration, the feeding of fat might, by

stimulating fat combustion, actually increase the removal rate of FFA from plasma without necessarily influencing the release of FFA from adipose tissue. Although changes in FFA concentration are believed to be entirely due to changes in their rate of release from adipose tissue, Bragdon and Gordon (13) have shown that nutritional status affects the removal rate of FFA and chylomicrons differently in different organs. Fat feeding after starvation might, by greatly stimulating fat combustion, have a sufficiently profound effect on the removal rate by some organ or organs to cause an increase in the overall disappearance rate of FFA.

Inherent to both of these possibilities and consistent with the striking sense of well-being reported by subjects refed with the fat meal is the assumption that fat fed after a period of fasting is more completely oxidized than fat fed after only an overnight fast. The adaptive changes occurring in response to starvation are only partially understood. The overall changes of starvation may be summarized as a conservation of carbohydrate and protein, and an increased facility in the combustion of fat (14). The rising concentrations of cholesterol and triglycerides (15) and FFA (4) during starvation reflect the increased transport and metabolism of fat. These changes are associated with enzymatic alterations (16, 17), and are probably under hormonal control (18-21). A similar metabolic change occurs in animals adapted to a high fat, low carbohydrate diet, and animals so adapted survive starvation longer and with less ketosis than those adapted to a high carbohydrate diet (22). It would seem reasonable to expect that the converse would also hold true, that a period of starvation would facilitate adaptation to a high fat, low carbohydrate diet. The present study offers evidence that such is the case. Studies of the hormonal changes of one of the subjects in the present paper will be reported separately (21). The beneficial effect of fasting and of carbohydrate restriction on the ketosis and lipemia of diabetics was well known before the insulin era (23, 24). A lesser degree of ketosis on the last of repeated episodes of starvation in humans (25) may indicate a similar increased efficiency of fat combustion. An inverse relationship between carbohydrate and fat metabolism is present

in many physiological and pathological conditions (26).

SUMMARY

When six normal subjects who had fasted overnight were fed a meal containing 60 g of fat but no carbohydrate, the plasma FFA increased slightly but consistently in all subjects within five hours after the meal.

A period of starvation of from two to seven days' duration caused an increase in plasma FFA concentration from an average of 0.38 after an overnight fast to an average of 1.85 mEq per L at the end of the fast. Variable increases in concentration of serum cholesterol and triglyceride were also noted.

A meal identical in composition to the control meal was given as the first meal terminating the starvation. In contrast to the control meal, this meal was followed by an abrupt decrease in the elevated concentrations of plasma FFA for five of the six subjects.

The present study thus reports a marked fall in FFA when a fat meal follows a period of starvation. This is in contrast to the small alterations in FFA following a fat meal after usual alimentation, and is a manifestation of the adaptive changes occurring during starvation and indicative of increased efficiency of fat metabolism.

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