The failure in lipogenesis induced by fasting: a new view

Since the establishment of the fact that fasting almost abolishes hepatic lipogenesis[1,2], investigators have looked for a mechanistic explanation of this inhibition along two lines, a deficiency of either co-factor levels or enzyme levels[3-5]. These two lines of approach have not thus far fully explained the mechanism responsible for suppression of hepatic lipogenesis during fasting. Therefore, this laboratory decided on a new approach and this work has implicated a heretofore unsuspected factor.

A 20 % homogenate of rat liver prepared in 0.25 *M* sucrose was centrifuged for 10 min at 600 × *g* to yield a cell- and nuclei-free supernatant which will be called the "homogenate". A particle-free fraction called the "supernatant" was prepared by centrifuging the homogenate for 1 h at 105,000 × *g*. The incubation system (except that the present system contained ATP (3 m*M*)), the incubation procedures, chemical analyses and ^{14}C analyses are described elsewhere[5].

Liver homogenates prepared from rats fasted for 24 h converted far less [1-^{14}C]-acetate to fatty acids than did those from normal fed rats (Table I). In the case of

TABLE I

EFFECT OF FASTING ON LIPOGENESIS BY RAT LIVER HOMOGENATE AND SUPERNATANT

Values are means ± standard error of mean.

Physiological state	*Number of rats used*	*Protein content per incubation flask*		*mμmoles [1-^{14}C]acetate converted to fatty acid*	
		Homogenate (mg)	*Supernatant (mg)*	*Homogenate**	*Supernatant**
Fed	6	75 ± 3.4	36 ± 1.4	354 ± 39.3	240 ± 28.2
Fasted	9	79 ± 4.9	38 ± 1.4	93 ± 12.9	147 ± 19.8

* In the case of each rat, homogenate and supernatant fractions were studied simultaneously thus permitting statistical evaluation of the data based on a paired-comparison method[6].

the fed rats the supernatant incorporated less [1-^{14}C]acetate into fatty acids than did the homogenate from which it came ($P < 0.01$)*; the opposite result was obtained with fasting rats, the supernatant synthesizing more fatty acids than the homogenate ($P < 0.01$)*.

These results suggested that in the liver of the fasted rat, the mitochondria or the microsomes or both suppress the lipogenic activity of the supernatant. To test this possibility further, the effect of each of these particulate fractions on the lipogenic activity of supernatant from fed rats was investigated (Table II). The cytoplasmic particles from fed rats stimulated the lipogenic activity of supernatant from fed rats ($P < 0.02$)* while the cytoplasmic particles from fasted rats inhibited it ($P < 0.01$)*. The mitochondria from both fed and fasted rats depressed lipogenesis by the supernatant from fed rats ($P < 0.01$)*, mitochondria from fasted rats being somewhat more inhibitory. The microsomes from both fed and fasted rats reduced the lipogenic activity of the supernatant from fed rats but the microsomes from the fasted rats had a far greater inhibitory action ($P < 0.001$)*. It should also be noted that the microsomes from fasted rats inhibited supernatant lipogenesis far more than did the mitochondria from these animals ($P < 0.01$)*.

* *P* values are calculated from paired-comparison statistics[6].

TABLE II

EFFECT OF HEPATIC CYTOPLASMIC PARTICULATE FRACTIONS ON THE LIPOGENIC ACTIVITY OF PARTICLE-FREE HEPATIC SUPERNATANT

Values are means ± standard error of mean

*Liver system**	*mμmoles [1-^{14}C]acetate converted to fatty acids***
"Fed" supernatant	296 ± 25.9
"Fed" supernatant + "fed" cytoplasmic particles	382 ± 24.0
"Fed" supernatant + "fasted" cytoplasmic particles	169 ± 22.8
"Fed" supernatant + "fed" mitochondria	172 ± 14.3
"Fed" supernatant + "fasted" mitochondria	108 ± 10.9
"Fed" supernatant + "fed" microsomes	222 ± 26.8
"Fed" supernatant + "fasted" microsomes	51 ± 8.4

* Cytoplasmic particles were isolated by centrifuging the nuclei-free homogenate at 105,000 × *g* for 60 min. Mitochondria and microsomes were isolated by modification of the method of SCHNEIDER AND HOGEBOOM[7]. The particulate fractions were suspended in a volume of the supernatant fraction equal to that from which they were derived. None of these particulate fractions synthesized fatty acids in the absence of the supernatant fraction.

** The values reported below are average ones for 7 rat pairs. The supernatant plus each of the particulate fraction additions were studied simultaneously for each rat pair, thus permitting statistical evaluation of the data based on a paired-comparison method[6].

It is concluded that the cytoplasmic particles of the liver cell of a fasting rat limit the lipogenic activity of the "particle-free" cytoplasm. The results indicate that the microsomes may be the major, if not the sole, site of this inhibitory action. This possibility is further supported by the finding that sonic treatment of the microsomes releases an inhibitory substance in a water-soluble form. It would seem therefore that, in addition to the possibilities that a deficiency of co-factors or loss of enzymes are responsible for the low rate of hepatic lipogenesis induced by fasting, another mechanism appears probable, the generation of an inhibitor by the microsomes.

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