Fatty acid oxidation affects food intake by altering hepatic energy status

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Friedman, Mark I., Ruth B. Harris, Hong J i, Israel Ramirez, and Michael G. Tordoff. Fatty acid oxidation affects food intake by altering hepatic energy status. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R1046–R1053, 1999.—Inhibition of fatty acid oxidation stimulates feeding behavior in rats. To determine whether a decrease in hepatic fatty acid oxidation triggers this behavioral response, we compared the effects of different doses of methyl palmitoxirate (MP), an inhibitor of fatty acid oxidation, on food intake with those on in vivo and in vitro liver and muscle metabolism. Administration of 1 mg/kg MP selectively decreased hepatic fatty acid oxidation but did not stimulate food intake. In contrast, feeding behavior increased in rats given 5 or 10 mg/kg MP, which inhibited hepatic fatty acid oxidation to the same extent as did the low dose but in addition suppressed fatty acid oxidation in muscle and produced a marked depletion of liver glycogen. Dose-related increases in food intake tracked dose-related reductions in liver ATP content, ATP-to-ADP ratio, and phosphorylation potential. The findings suggest that a decrease in hepatic fatty acid oxidation can stimulate feeding behavior by reducing hepatic energy production.

feeding behavior; metabolism; liver; adenosine 5'-triphosphate; methyl palmitoxirate

A VARIETY OF EVIDENCE indicates that the oxidation of fatty acids influences feeding behavior (see Ref. 4), with perhaps the most direct support from experiments showing that rats increase food intake after treatment with agents that inhibit the oxidation of fatty acids (5, 24). Administration of either mercaptoacetate (MA), which suppresses fatty acid oxidation by inhibiting the acyl-CoA dehydrogenases that catalyze mitochondrial β-oxidation (see Ref. 24), or methyl palmitoxirate (MP), which reduces fatty acid oxidation by inhibiting the intramitochondrial transport of fatty acids (1, 34, 35), stimulates feeding behavior in rats (e.g., Refs. 5, 7, 18). The effect of these inhibitors on food intake is most evident when the maintenance diet is high in fat or glucose utilization is impaired (7, 8, 27), that is, when fats are a major source of metabolic energy. This further suggests that a decrease in fatty acid oxidation underlies the eating response to administration of MA or MP.

The increase in feeding behavior seen after inhibition of fatty acid oxidation appears to be triggered by a signal generated in the liver, because total vagotomy, visceral deafferentation induced by systemic capsaicin, or hepatic branch vagotomy prevents or attenuates the response to MA (13, 20, 21). However, because MA was given systemically in these denervation experiments, it is unclear whether MA stimulates eating by inhibiting the oxidation of fatty acids in liver or whether the metabolic consequences of MA acting in other tissues are detected by a hepatic sensor. In the experiments described below, we attempted to resolve this question by using MP to selectively inhibit fatty acid oxidation in liver.

MP suppresses fatty acid oxidation by inhibiting carnitine palmitoyltransferase I (CPT I), which transports long-chain fatty acids into mitochondria (1, 32, 34). This mechanism of action apparently underlies the behavioral effect of MP, because provision of medium-chain fatty acids, which do not depend on CPT I for intramitochondrial transport and oxidation, prevents the eating response (5). Presumably, because the liver and muscle isoforms of CPT I have different affinities for MP (12), low doses of MP markedly inhibit CPT I in liver but have relatively little effect on CPT I in muscle (32), the other major tissue that oxidizes fatty acids. We took advantage of this differential sensitivity of liver and muscle CPT I and compared the dose-response relationships between the effects of MP on food intake with those on metabolism to determine whether a decrease in fatty acid oxidation restricted to the liver stimulates eating in rats.

METHODS AND PROCEDURES

Animals and diets. Adult male CD Sprague-Dawley rats (Charles River; Wilmington, MA) weighing 350–450 g at the time of testing, were used for all experiments. Rats were housed individually in temperature-controlled (22°C) rooms that were maintained on a 12:12-h light-dark cycle (lights on at 0700). Rats were fed a high-fat, low-carbohydrate diet with 63 and 13% of energy as fat (corn oil) and carbohydrate, respectively (19), and given tap water ad libitum except when noted otherwise. Rats were fed the experimental diet for 10–14 days before testing. Food intakes were measured to the nearest 0.1 g, corrected for spillage.

Inhibitor treatment. MP (methyl 2-tetradecylglycidate) was given to rats by gavage tube at 1–2 h after the start of the daylight period. MP was suspended in a methyl cellulose (0.05%) vehicle, and both MP and vehicle were given in a volume of 3 ml/Kg. MP suspensions were sonicated and mixed by vortexing before gavage. Groups of rats receiving different doses of MP (or vehicle) were matched on the basis of body weight.

Blood and tissue assays. Blood was collected in heparinized tubes either from the tip of the tail (for repeated sampling) or from the trunk after decapitation. Plasma obtained after centrifugation was analyzed for glucose using a Beckman glucose analyzer (glucose oxidase) and for total ketone bodies (β-hydroxybutyrate plus acetoacetate), free (unesterified) fatty
acids (FFA), triglycerides, and glycerol using enzymatic assays with fluorometric detection (see Ref. 16). Liver glycogen was measured using an enzymatic procedure (10).

For measurement of liver ATP, ADP, and Pi, rats were anesthetized by subcutaneous injection of ketamine (100 mg/ml) plus acepromazine maleate (1 mg/ml). A sample of the median lobe of the liver was removed through a midline incision, immediately freeze-clamped in aluminum blocks cooled in liquid nitrogen, and then submerged in liquid nitrogen. Samples were stored at −70°C and then assayed for adenine nucleotides by HPLC (11, 23) and for Pi using a commercial kit (no. 360–3; Sigma, St. Louis, MO). Phosphorylation potential was calculated as [ATP/(ADP × Pi)].

In vitro fatty acid metabolism. Rats were decapitated, and samples of liver tissue and diaphragm (muscle) were collected through a midline incision. One portion of liver was frozen in acetone and dry ice for later determination of glycogen. Another portion of liver and the diaphragm sample were sliced, and 90- to 110-mg pieces were incubated in a bicarbonate-buffered Krebs-Ringer medium containing 5 mM glucose, 0.5 mM palmitate, 2% BSA, and either 0.3 or 0.6 µCi of [1-14C]palmitate (for liver and diaphragm tissue, respectively). After 2 h, 0.2 ml of hyamine was added to the center wells of the incubation flasks (to trap CO2), and cellular reactions were terminated by addition of 0.5 ml of 1 N H2SO4 to the media. CO2 was collected for 30 min. Total lipids were obtained by extraction of the tissue slices with heptane. Acid water-soluble products (AWSP) were extracted from the media with chloroform:methanol:acid NaCl. Incorporation of radioactivity into CO2, AWSP, and total lipids was measured using a liquid-scintillation spectrometer.

Data analysis. Dose-response data from experiments involving more than two dose levels were analyzed by ANOVA. Time course data were analyzed by ANOVA with repeated measures. All other data involving two-group comparisons were analyzed using the Student’s t-test. Post hoc comparisons, using a critical difference test or Newman-Keuls, were made only when the main or interaction terms of the ANOVA were statistically significant at P < 0.05. Only the results of post hoc comparisons with a P < 0.05 are reported.

RESULTS

Ad libitum food intake. To determine the dose-response relationship between MP and feeding behavior, 40 rats (n = 10/group) were given either vehicle or 1, 5, or 10 mg/kg MP, and food intakes were measured every 2 h for 8 h. Administration of MP increased food intake of rats in a dose-related fashion during the 8-h observation period [Fig. 1; F(12,144) = 4.3, P < .0001]. Compared with those given vehicle or 1 mg/kg MP, rats given the two larger doses of MP increased food intake starting, respectively, 4 and 6 h after MP treatment (P < 0.05). Food intakes of rats given the lowest dose (1 mg/kg) were similar to those of rats given vehicle.

Plasma fuels and food intake. The effects of MP on circulating metabolic fuels and food intake were assessed by sampling plasma fuels just before the feeding test, a protocol that circumvents the confounding effect of food ingestion on these metabolic measures (e.g., Refs. 5–7). One week after the first experiment, the same rats were deprived of food, and tail blood was sampled just before the animals were retreated with vehicle or MP. Additional blood samples were collected 3 and 5 h later. Food was returned (at 5 h), and food intakes were measured 3 h later. The feeding test was started at 5 h posttreatment because the first experiment showed that the eating response to the higher doses of the inhibitor is initiated at about this time.

As shown in Figs. 2 and 3, MP altered food intake and plasma glucose and FFA concentrations in a dose-related fashion, but its effect on plasma ketone body levels was not dose related. MP decreased plasma glucose and increased plasma FFA [F(6,72) = 10.8 and 11.9 for glucose and FFA, respectively, P < 0.00001]. Plasma glucose and FFA levels of rats given vehicle or 1 mg/kg MP were similar and did not change significantly from baseline (0 h) over the 5-h observation period. However, 3 and 5 h after administration of 5 or 10 mg/kg MP, plasma glucose levels decreased and FFA concentrations increased relative to treatment with vehicle or 1 mg/kg MP and relative to baseline values. The effect of 5 mg/kg MP on glucose and FFA levels was similar to that of 10 mg/kg MP. MP treatment decreased plasma ketone body levels [F(6,72) = 19.0, P < 0.00001]. In rats given vehicle, plasma ketone body concentrations increased significantly from baseline (0 h) during the 5-h period after treatment. In MP-treated rats, ketone body levels decreased markedly from baseline during this period and were significantly lower than those in vehicle-treated rats at both the 3- and 5-h time points. Administration of MP had no significant effect on plasma concentrations of glycerol or triglycerides (data not shown).

When rats were refed after the last blood sample, those given MP increased food intake in a dose-related fashion [F(3,36) = 10.0, P < 0.0001; Fig. 3]. Whereas rats given 1 mg/kg MP ate the same amount of food as those given vehicle, rats given the higher doses of MP consumed more food than did rats treated with vehicle.
or 1 mg/kg. In addition, rats given 10 mg/kg MP ate more than those treated with 5 mg/kg.

Plasma glucose and food intake. The previous experiment showed that doses of MP that decreased plasma glucose concentration also stimulated food intake. Because a reduction in plasma glucose is thought to be a signal that triggers feeding behavior (e.g., Ref. 30), we performed an experiment to determine whether preventing the decline in plasma glucose level after MP treatment would attenuate the eating response to the inhibitor. Twenty-one rats were deprived of food and given vehicle. Five hours later, blood samples were taken from the tips of their tails (for analysis of glucose), food was returned, and intakes were measured 3 h later. Two or three days later, rats were retested, except that they were given 10 mg/kg of MP instead of vehicle and subcutaneously injected 4 h later with either 0.5 ml isotonic saline or 25% glucose to raise systemic glucose levels.

Under control (vehicle) conditions, plasma glucose concentrations ranged from 6.5 to 7.6 mM. Although rats injected with glucose had higher plasma glucose levels 5 h posttreatment with MP than did those injected with saline (6.7 ± 0.1 vs. 6.3 ± 0.2 mM), this difference was not statistically significant, because glucose values were somewhat variable in the two groups. To assess the relationship between plasma glucose level and the eating response to MP treatment, we compared the results from glucose-injected rats that had plasma glucose concentrations ≥6.5 mM (n = 7) with those from saline-injected rats that had glucose levels <6.5 mM (n = 7). A plasma glucose concentration of 6.5 mM was chosen as the criterion because this was the lowest level found in vehicle-treated rats. As shown in Table 1, rats injected with glucose had significantly greater plasma glucose concentrations than did those given saline (t(12) = 4.7, P < 0.0005) and showed less of a decrease in plasma glucose from control (vehicle).
levels $[t(12) = 3.7, P < 0.005]$ than did those injected with saline. Despite these differences in plasma glucose, food intakes after MP treatment in saline- and glucose-injected rats were similar considered either in absolute terms or as a change from control (vehicle) levels. Rats injected with saline ($n = 3$) and glucose ($n = 4$) that did not meet the criterion described above did not differ significantly with respect to plasma glucose level, change in plasma glucose (from vehicle-treated control condition), or eating response to MP.

Tissue FFA metabolism. Given the observation that all doses of MP decreased plasma ketone bodies, but only the high doses affected plasma glucose and fatty acids, it appeared that the lowest dose of MP had a more selective effect on liver fatty acid oxidation than did the higher doses. To determine whether the inhibition of fatty acid oxidation induced by the low dose was relatively restricted to liver, we examined the effects of low and high doses of MP on fatty acid metabolism in liver and muscle in vitro. To relate these metabolic measures to the effects of MP on food intake, samples of liver and muscle tissue were collected under conditions in which different doses of MP were shown to differentially affect feeding behavior. Thirty rats ($n = 10$/group) were deprived of food and given either vehicle or 1 or 10 mg/kg MP. Five hours later (by which time rats initiate eating in response to the high dose), rats were killed for collection of liver and diaphragm tissue and measurement of liver glycogen and in vitro FFA metabolism.

MP treatment reduced liver glycogen content $[F(2,27) = 32.6, P < 0.00001$; Fig. 4]. Both doses of MP significantly reduced liver glycogen, and the high dose decreased glycogen significantly more than did the low dose (78 vs. 40%). Administration of MP reduced the incorporation of $^{14}$C (from [1-14C]palmitate) in liver tissue into CO2 and AWSP and increased the incorporation into total lipids $[F(2,27) = 5.9, 26.6, and 3.8$ and $P < 0.01, 0.00001$, and 0.05 for CO2, AWSP, and total lipids, respectively; Fig. 5]. The effects of the two doses of MP on incorporation of radioactivity into CO2 and AWSP were similar (a decrease of ~25 and 55%, respectively), but only the high dose had a significant effect on incorporation into total lipids. In muscle (diaphragm) tissue, MP significantly reduced $^{14}$C incorporation into CO2 $[F(2,27) = 10.8, P < 0.001]$, but only the high dose was effective, decreasing incorporation by 32%. There was no significant effect of MP treatment on incorporation of radiolabel into AWSP or total lipids in diaphragm.

Hepatic energy status. The results of the previous experiment showed that different doses of MP, which are differentially effective in stimulating food intake, decreased hepatic fatty acid oxidation to the same extent. Fatty acids are an important hepatic fuel (14, 15), and recent evidence suggests that a decline in liver ATP content generates a signal that triggers eating behavior (3, 11). Therefore, to determine whether doses of MP that differentially affect food intake also have different effects on liver energy status, we measured ATP, ADP, and Pi in 24 rats ($n = 8$/group) 5 h after administration of vehicle or 1 or 10 mg/kg MP. As in the previous experiments, rats were deprived of food after treatment to avoid confounding the metabolic measures with consequences of food ingestion.

Administration of the high, but not low, dose of MP reduced hepatic energy status (Fig. 6). Overall, MP decreased liver ATP content and reduced the hepatic ATP-to-ADP ratio and phosphorylation potential $[F(2,21) = 5.3, 13.2, and 9.1$ and $P < 0.02, 0.001$, and 0.002, respectively]. These effects were attributable to the high dose of MP. Only the 10-mg/kg dose significantly reduced liver ATP relative to vehicle treatment. Also, the hepatic ATP-to-ADP ratio and phosphorylation potential were lower only in rats given 10 mg/kg MP compared with those given vehicle or 1 mg/kg. Rats given the low dose did not differ from those given vehicle on any of these measures. MP treatment also

\begin{table}[h]
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\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
 & Plasma Glucose, mM & ΔPlasma Glucose, mM & Food Intake, g/3 h & ΔFood Intake, g/3 h \\
\hline
Saline & 6.08 ± 0.13 & -0.93 ± 0.07 & 1.4 ± 0.4 & 0.8 ± 0.3 \\
Glucose & 6.99 ± 0.14 & -0.24 ± 0.17 & 1.9 ± 0.4 & 1.2 ± 0.4 \\
\hline
\end{tabular}
\caption{Effect of exogenous glucose on plasma glucose and food intake of rats treated with MP}
\end{table}
reduced liver glycogen content \( F(2,21) = 34.2, P < 0.00001 \). As in the last experiment, both doses of MP depleted liver glycogen, and the high dose reduced it more than twice as much as did the low dose (71 vs. 27%).

**DISCUSSION**

These experiments were conducted to determine whether a decrease in fatty acid oxidation restricted to the liver stimulates feeding behavior in rats. In vivo and in vitro metabolic measures verified that a low dose of MP (1 mg/kg) selectively decreased fatty acid oxidation in the liver. Despite this inhibition, MP given at this dose did not stimulate food intake. In contrast, feeding behavior increased after rats were given higher doses of MP, which inhibited hepatic fatty acid oxidation to the same extent as did the low dose but in addition suppressed fatty acid oxidation in muscle. Whereas the eating response to MP treatment could not be explained by changes in hepatic fatty acid oxidation, the behavioral effect of MP was found to track reductions in liver glycogen content and hepatic energy status. These findings indicate that a decrease in hepatic fatty acid oxidation per se may not be sufficient to trigger eating behavior. Instead, the results suggest that, when combined with a limited capacity to oxidize alternative fuels, a decrease in hepatic fatty acid oxidation can stimulate feeding behavior by limiting hepatic energy production.

**Metabolic effects of MP treatment**. The metabolic effects of MP treatment observed in these experiments are consistent with the inhibitor’s actions that have been described previously (5, 7, 18, 31–35). Although high doses of MP inhibit CPT I in liver and muscle, low doses, like the 1 mg/kg dose used in the present experiments, act primarily on CPT I in liver (32), possibly because MP has a greater affinity for the liver isoform of CPT I than does for the muscle isoform (12). This selective effect of low doses of MP accounts for the observation that, whereas both low and high doses inhibited fatty acid oxidation in liver tissue, only the high dose suppressed fatty acid oxidation in diaphragm. In keeping with the greater susceptibility of liver CPT I to inhibition by MP, low and high doses of the inhibitor suppressed hepatic fatty acid oxidation maximally. As a consequence, the different doses also

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Fig. 5. Effects of MP on in vitro fatty acid metabolism in liver and diaphragm slices. Rats were deprived of food on treatment, and tissue samples were collected 5 h later. Values are rates of incorporation of \(^{14}C\) (from \([1-^{14}C]\)palmitate) into \(CO_2\) (top), acid water soluble products (AWSP; middle), and total lipids (bottom). Values are means ± SE; \(n = 10\) rats/group. Values labeled with different letters are significantly different \((P < 0.05)\).

Fig. 6. Effects of MP on liver ATP, ATP/ADP (top), phosphorylation potential, and glycogen (bottom). Values are means ± SE; \(n = 10\) rats/group. Values labeled with different letters are significantly different \((P < 0.05)\).
produced an equivalent and maximal decrease in liver ketogenesis, judging by the similar declines in plasma ketone body levels. Given the differences in the site of action of low and high doses of MP, the increase in plasma FFA in rats given the high, but not low, doses of MP appears to result from a decrease in the uptake and/or utilization of fatty acids primarily by muscle as opposed to liver.

Many of the metabolic effects of MP can be understood in terms of the glucose-fatty acid cycle described by Randle et al. (17), in which a decrease in the oxidation of fatty acids is met by a compensatory increase in the oxidation of glucose and vice versa. This reciprocal relationship between the metabolism of fatty acids and glucose has been demonstrated in muscle, in which glucose oxidation increases markedly after treatment with MP (31, 35). The decrease in blood glucose after administration of MP results in part from the enhanced rate of glucose oxidation in muscle and also in part from suppression of hepatic gluconeogenesis, which is fueled largely by the oxidation of fatty acids (33). As a result of the reduction in gluconeogenesis, liver glycogen must be mobilized to meet the increased demand of muscle tissue for glucose, and liver glycogen content decreases accordingly. In the present experiments, the decline in plasma glucose after MP treatment was seen only with the higher doses of the inhibitor, because these doses, which depressed muscle fatty acid oxidation, probably also increased muscle glucose oxidation. Presumably, the low dose of MP did not decrease plasma glucose concentrations because it failed to inhibit muscle fatty acid oxidation and produce a compensatory change in glucose utilization. The extraordinary depletion of liver glycogen in rats given the high dose of MP most likely can be attributed to enhanced glucose utilization by muscle. However, such a mechanism does not explain the decrease, albeit smaller, in liver glycogen in rats given the low dose of MP because there was no evidence that muscle was affected at this dose (see also Ref. 32). It is possible that the reduction in liver glycogen in rats given the low dose of MP resulted from an enhanced rate of glucose oxidation by liver. Such an increase in hepatic glucose oxidation would help explain how liver energy production was maintained in rats given the low dose of MP despite the inhibition of hepatic fatty acid oxidation.

Relationship between the metabolic and behavioral effects of MP. Scharer and colleagues (25) have suggested that changes in hepatic fatty acid oxidation produce a signal that controls food intake. They hypothesize that this signal is generated when ketone bodies, which are synthesized by the hepatocellular oxidation of fatty acids, are released into the extracellular compartment and stimulate vagal afferent neurons innervating the liver (25). The present results contradict this hypothesis because feeding behavior after MP treatment was not tied to either hepatic fatty acid oxidation or to ketogenesis. Administration of 1 or 10 mg/kg MP to rats induced a marked and equivalent inhibition of hepatic fatty acid oxidation, but only the high dose increased food intake. Inhibition of fatty acid oxidation was demonstrated under conditions similar to those used in the behavioral tests and within a time frame in which the behavioral responses were observed. Suppression of fatty acid oxidation was evidenced by a large decline in circulating ketone bodies and a reduced incorporation of $^{13}$C (from $[1-^{13}$C]$\text{palmitate}$ into CO$_2$ and AWSP in liver slices. Under the conditions used in the in vitro experiments with liver tissue, it seems likely that $^{13}$C recovered in AWSP includes ketone bodies synthesized from the $[1-^{13}$C]$\text{palmitate}$ substrate. That both low and high doses of MP decreased plasma ketone body levels and apparently suppressed hepatic ketogenesis to the same degree argues against the notion that blood or liver ketone body concentrations are monitored by the nervous system to elicit eating behavior. However, because injection of ketone bodies transiently decreases food intake in rats (e.g., Ref. 13), it remains possible that the level of ketone body or some aspect of their hepatic metabolism may play a role in satiety.

Other metabolic effects of MP besides hepatic fatty acid oxidation varied as a function of dose in the same manner as did food intake. Administration of high doses of MP decreased plasma glucose concentrations, whereas treatment with the low dose had no such effect. Decreased blood glucose has long been thought to stimulate eating (e.g., Ref. 30). However, in the present case, the decline in plasma glucose after the high dose did not appear to underlie the eating response, because injections of glucose that increased plasma glucose levels did not prevent the increase in food intake after MP treatment. This conclusion is consistent with other results showing that MP treatment potentiates the eating response to administration of other metabolic inhibitors independently of changes in plasma glucose levels (7, 18). In addition, the decline in plasma glucose after MP treatment in the present experiment was relatively small, leaving circulating levels well above those needed to elicit eating behavior during insulin-induced hypoglycemia (i.e., below 4 mM plasma) (30).

MP treatment decreased liver glycogen content, and the magnitude of this depletion depended on the dose of MP; the high dose decreased glycogen content at least twice as much as did the low dose. Several investigators have suggested that a reduction in liver glycogen content generates a signal that stimulates food intake (2, 22). In general, the present findings are consistent with this hypothesis because the high dose of MP, which produced the greatest depletion of liver glycogen, increased feeding behavior, whereas the low dose did not. However, the low dose of MP had a substantial effect on liver glycogen (~30–40% decrease) yet had no effect on food intake. In addition, previous experiments have shown that administration of MP to rats synergistically increases the eating response to injection of 2,5-anhydro-o-mannitol (2,5-AM), which inhibits glycogenolysis and prevents the depletion of liver glycogen otherwise produced by MP (18). These and other findings (7) argue strongly against a causal role of glycogen depletion in the eating response to MP treatment.
Of the metabolic parameters examined, changes in hepatic energy status best paralleled the behavioral responses to different doses of MP. Administration of the high dose of MP decreased liver ATP concentration, the hepatic ATP-to-ADP ratio, and phosphorylation potential, whereas the low dose had no effect on these measures. These changes in ATP, ADP, and Pi, caused by treatment with the high dose of MP are indicative of a decrease in ATP production. Studies with 2,5-AM and other metabolic inhibitors suggest that a reduction in liver ATP or a related change in ATP metabolism triggers eating behavior in rats (3, 11). The present experiments are the first to show that administration of an inhibitor of fatty acid oxidation that stimulates feeding behavior also decreases liver energy production, and thus provide additional evidence that changes in hepatic energy status control food intake. The eating response to injection of 2,5-AM is associated with a larger decrease in ATP (11, 18) than that observed after MP treatment in the present study. Whether this reflects the operation of different signaling mechanisms or the more acute action of 2,5-AM compared with MP remains to be determined.

Perspectives

The results suggest that no single change in liver metabolism at the substrate level generates a signal to initiate food intake. Instead, the findings indicate that a combined decrease in the oxidation of different fuels can lead to a reduction in hepatic energy status, which in turn triggers eating behavior (see Ref. 3). The liver relies in large part on the oxidation of fatty acids for its energy needs (14, 15); however, when the capacity to oxidize fatty acids is limited, the liver must use other fuels to maintain energy status. In addition to amino acids (15), glucose derived from the breakdown of liver glycogen could be used as an alternative fuel. However, when both fatty acid oxidation is insufficient and the supply of alternative fuels is limited or inaccessible, hepatic energy production declines. It is under these circumstances that a hepatic signal to eat is generated.

The current findings are consistent with this scenario, although it is possible that under other conditions in which fatty acid oxidation is suppressed different mechanisms may be involved. In the present studies, rats had a relatively low liver glycogen content to begin with because they were fed a high-fat, low-carbohydrate diet (e.g., Ref. 18). Treatment with the high dose of MP largely depleted this small store of liver glycogen, presumably by increasing glucose demand from muscle. According to the model described above, the suppression of liver fatty acid oxidation combined with a depleted liver glucose reserve led to a decrease in hepatic energy production and an eating response. In comparison with the high dose, administration of the low dose of MP suppressed liver fatty acid oxidation to the same extent but did not deplete hepatic glycogen reserves nearly as much. This differential effect on liver glycogen content presumably resulted because the low dose of MP did not suppress muscle fatty acid oxidation and consequently did not produce a compensatory increase in muscle glucose oxidation. The relatively larger glycogen reserve of rats given the low dose of MP supplied fuel (glucose) for the liver, which, when oxidized, forestalled a decline in hepatic energy production and the generation of a signal to initiate feeding behavior. In this way, the response of rats given 1 mg/kg MP resembles that of rats fed a low-fat, high-carbohydrate diet and given 10 mg/kg MP, namely, a relatively small decline in liver glycogen (7), in this case from a high level, and no increase in food intake (7, 8).

For the model outlined here, a decrease in hepatic fatty acid oxidation elicits feeding behavior when alternative fuels are not sufficiently available and/or oxidizable to maintain energy production in the liver. In many cases, glycogen would provide the alternative source of hepatic fuel in the form of glucose, although other oxidizable substrates (e.g., lactate or amino acids) might serve a similar role. Circulating glucose seems unlikely to be used as a hepatic fuel under these conditions because liver metabolism is geared toward glucose output rather than uptake in the face of increased glucose utilization by muscle.

It is important to emphasize that, in terms of the perspective outlined here, it is the utilization of glycogen as a fuel source, rather than the absolute level of liver glycogen, that is crucial. This distinction between access to the hepatic glycogen reserve and the size of that reserve is illustrated clearly by the finding that administration of 2,5-AM potentiates the eating response to MP while at the same time preventing the depletion of glycogen (18). A role for liver glycogen in the control of food intake has been suspected for many years (2, 22), but the relationship between this metabolic parameter and feeding behavior is inconsistent (6, 18, 26, 28). From the analysis presented here, this inconsistency could be explained by the use of an inappropriate measure of liver glycogen (i.e., size of the reserve), as well as by the indirect contribution that the glycogen reserve makes in maintaining hepatic energy production.

Under some circumstances, an increase in the oxidation of fatty acids by liver could maintain hepatic energy production and forestall eating behavior when the availability and/or oxidation of other substrates such as glycogen is limited. The normalization of food intake seen when hyperphagic diabetic rats are fed a high-fat diet may be a case in point. These animals have extremely low glycogen levels (e.g., Ref. 6), display very high rates of fat oxidation (4, 6), and, unlike their counterparts fed a low-fat diet, have normal liver ATP levels (9). In the context of the model presented here, it is important to emphasize that for hepatic fatty acid oxidation to prevent eating, it must proceed at a rate that supports the energy status of the liver. Feeding behavior would still be triggered if the increase in fatty acid oxidation were not of sufficient magnitude. Such a situation may obtain during fasting, perhaps the most fundamental condition that stimulates feeding behavior. In the absence of food, liver glycogen is rapidly depleted, and whereas fatty acid oxidation increases, it
does not increase enough to prevent a decline in liver ATP production (29).

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