Suppression of food intake, body weight, and body fat by jejunal fatty acid infusions

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Cox, James E., William J. Tyler, Alan Randich, Gary R. Kelm, Satinder S. Bharaj, Ronald J. Jandacek, and Stephen T. Meller. Suppression of food intake, body weight, and body fat by jejunal fatty acid infusions. Am. J. Physiol. Regulatory Integrative Comp. Physiol. 278: R604-R610, 2000.—Three experiments investigated effects of jejunal lipid infusions given on 4 or 21 consecutive days in adult, male Sprague-Dawley rats. In experiment 1, 7-h infusions of linoleic or oleic acid (0.2 ml/h for 7 h; total load = 11.5 kcal) on 4 consecutive days reduced total intake (ad libitum consumption of the liquid diet Boost, Mead Johnson, plus load) by \sim 15% and decreased weight gain compared with 4-day tests with saline administration. In *experiment 2*, linoleic acid at 0.1 ml/h for 7 h (5.7 kcal) was ineffective, whereas the same load delivered in 3.5 h produced effects similar in magnitude to those in the first experiment. In experiment 3, jejunal infusions of linoleic acid (0.2 ml/h for 7 h) on 21 consecutive days reduced mean total intake by 16%, body weight by 10%, and carcass fat by 48% compared with controls receiving saline. The net decrease in caloric intake may reflect the combined activation of pre- and postabsorptive mechanisms, and it suggests a possible treatment for obesity.

linoleic acid; oleic acid; satiety; small intestine

OBSERVATIONS OF REDUCED FOOD intake resulting from infusions of lipids into the small intestine have suggested the existence of intestinal satiety mechanisms sensitive to intraluminal lipids (3, 9, 25). Although some previous reports are vulnerable to the criticism (6, 10) that infusion rates were too rapid to be of physiological significance, other studies have found suppression of intake even when infusion rates were below published estimates of the rate of gastric emptying after lipid loads (e.g., Ref. 25). Potential clinical significance of the satiating effect of intraintestinal lipids is suggested by observations that the amount of intake suppression may exceed the caloric value of the load. Such overcompensation has been observed in both rats (3, 16, 25) and human subjects (23). If sustained with repeated dosing, this effect has obvious potential for promoting weight loss, although little evidence is available for evaluating this possibility. In multipleday studies on rats, both negative (7) and positive results (3) have been reported. In the experiments described below, adult, male Sprague-Dawley rats received slow jejunal infusions of free linoleic or oleic acid on either 4 or 21 consecutive days. Loads as small as 6.5% of baseline caloric intake delivered at 0.2 ml/h (0.027 kcal/min) suppressed voluntary consumption in excess of the load and reduced weight gain and body fat.

METHOD

General procedures. Procedures were approved by the Institutional Animal Care and Use Committee at the University of Alabama at Birmingham. Adult, male Sprague-Dawley rats were obtained from Harlan. Rats were adapted for \sim 3 wk to consuming a nutritionally complete liquid diet (vanilla-flavored Boost, Mead Johnson, 1 kcal/ml) from graduated sipper tubes in the test chambers. Chambers were constructed from Plexiglas cylinders 12 in. in diameter.

Before surgery, rats received injections of atropine methyl nitrate (0.15 mg ip) and sulfamethoxazole-trimethoprim (0.1 ml im) and were anesthetized with pentobarbital sodium (50 mg/kg ip). After a laparotomy, a microrenathane catheter (MRE 065, Braintree Scientific, Braintree, MA) was inserted into the jejunum, 50 cm from the ileocecal junction (distance from the pylorus was \sim 65 cm). It was secured with two purse-string sutures (6-O silk) around the point of entry, and two sutures were glued to the catheter and tied to the serosa. A piece of Marlex mesh (Bard, Cranston, RI) was secured over the entry wound to facilitate healing. The other end of the catheter was threaded through an opening in the abdominal wall and then subcutaneously to an exit on the dorsal surface of the neck, where it was secured to underlying muscles with silk sutures and Marlex mesh and capped with monofilament fishing line.

After 1 wk of recovery, rats underwent $\sim 2-3$ wk of additional adaptation, which included jejunal infusion of normal saline (0.2 ml/h) from a syringe pump. Swivels in the delivery system allowed rats freedom of movement within the test chambers.

In all experiments, rats were maintained on a 12:12-h light-dark cycle with lights out from 10 AM to 10 PM. Rats were maintained in the test chambers from 9 AM to 4 PM, and they had access to liquid diet from 10 AM to 4 PM in the chambers and then continuously in their home cages until 9 AM. Thus food was available for 23 h/day. Rats were weighed every morning before the start of that day's test.

Data analysis focused on whether infusions of free fatty acids 1) suppressed intake compared with tests with saline infusion, 2) suppressed caloric intake in excess of load, and 3) reduced body weight and fat relative to controls. Statistical techniques were ANOVA, *t*-tests for matched and indepen-

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dent samples (1 tailed), and Holm's test (1 tailed). The latter was used as a multiple comparison procedure (21) when effects of lipid infusions were assessed at more than one time point [test statistic referred to as t'(11)].

Experiment 1. All rats (n = 7) underwent an initial set of tests involving infusion of commercial-grade linoleic acid (Sigma; 60% linoleic acid, 30% oleic acid, and 10% nonspecified fatty acids) followed by a second set in which oleic acid (Sigma; 95% oleic acid, 5% nonspecified fatty acids) was used. A given set spanned 2 consecutive weeks, such that a rat received in randomized order lipid infusions during 1 wk and saline during the other. Within each week, rats received 7-h infusions on 4 consecutive days. Infusions began at 9 AM and continued at 0.2 ml/h until 4 PM, for a total load of 1.4 ml (~11.5 kcal). Cumulative food intake was measured 1, 3, 6, and 23 h after its initial presentation in the test chamber.

Experiment 2. This experiment investigated the effect of reducing the total load of linoleic acid by half compared with *experiment 1* by altering either the rate or total time of delivery. Rats underwent two sets of feeding tests that were otherwise identical to those in the previous study. In the first set of tests (n = 10), rats received jejunal linoleic acid infusions at 0.1 ml/h for 7 h, and in the second set (n = 9) at 0.2 ml/h for 3.5 h, for a total load of 0.7 ml (~5.7 kcal). In both cases, infusions began 1 h before presentation of food, as before.

Experiment 3. This study used the same surgical infusion and feeding protocols as *experiment 1*, but each rat received the same infusate on 21 consecutive days. Rats were assigned to two infusion conditions, linoleic acid (n = 6) or saline (n = 8), in a between-groups design. Food intake was measured each day 6 and 23 h after initial presentation.

After completion of the study, animals received an overdose of pentobarbital sodium. Carcasses were frozen, pending body composition analysis. They were thawed at room temperature, and the gastrointestinal tract was removed. Water content was determined by drying to constant mass at 70°C. Fat was extracted from dried carcasses with petroleum ether in a Soxhlet apparatus to determine content of fat-free dry mass (FFDM) and fat (4).

RESULTS

Experiment 1. Infusion of linoleic acid at 0.2 ml/h (0.027 kcal/min) for 7 h had similar effects on food intake on each of 4 consecutive days (Fig. 1). Because a three-factor (infusate \times day \times time) repeated-measures ANOVA revealed no significant effects involving the day factor (all P values > 0.15), results were pooled across days in Fig. 2. The infusate main effect [F(1,6) =31.85, P < 0.005] and the infusate \times time interaction [F(3,18) = 15.12, P < 0.0001] were significant, as were the differences in cumulative intake between saline and linoleic acid tests at the 1-, 3-, 6-, and 23-h points [Fig. 2*A*; *t*′(6) = 2.31, 5.95, 6.56, and 4.42, respectively; all P values < 0.05]. Moreover, infusion of linoleic acid produced a decrease in total caloric intake (defined as liquid diet ingested plus load) at 3, 6, and 23 h [Fig. 2*B*; t'(6) = 4.09, 3.56, and 2.53, respectively; all P values < 0.05]. Consumption between the 6- and 23-h points was approximately equal on saline and linoleic acid tests. Cumulative suppression did not change significantly between those two times [t(6) = 0.59, P > 0.40]. For 23-h intake, average suppression of total intake was 15.3 kcal, equivalent to 15% of intake on saline-



Fig. 1. Mean cumulative food intake 1, 3, 6, and 23 h after presentation of liquid diet in rats (n = 7) receiving jejunal infusions of linoleic acid or saline at 0.2 ml/h for 7 h on 4 consecutive days. *A*, *day* 1; *B*, *day* 2; *C*, *day* 3; *D*, *day* 4.



Fig. 2. *A*: cumulative food intake 1, 3, 6, and 23 h after presentation of liquid diet in rats (n = 7) receiving jejunal infusions of linoleic acid or saline at 0.2 ml/h for 7 h on 4 consecutive days. Values shown are means pooling over days. *P < 0.05 and **P < 0.01 for comparison of linoleic acid and saline tests. *B*: mean differences in intake (\pm SE) between saline and linoleic acid tests (solid line) compared with load delivered (dashed line). *P < 0.05 for comparison of mean suppression vs. load.

infusion tests. The weight gain rats exhibited when receiving saline was eliminated by the lipid infusions [Fig. 3; t(6) = 6.37, P < 0.001 for the difference in weight gain over 4 days].

Effects of oleic acid infusions (11.5 kcal/day) were almost identical to those produced by linoleic acid. Degree of suppression did not differ across days



Fig. 3. Mean changes (\pm SE) in body weight when rats (n = 7) received linoleic acid or saline on 4 consecutive days. ** P < 0.01 for comparison of weight gain on *day 4*.

[F(3,18) = 0.79, P > 0.50], and the infusate main effect [F(1,6) = 59.23, P < 0.001] and infusate \times time interaction [F(3,18) = 31.82, P < 0.00005] were significant. When data were pooled across the 4 test days, consumption was significantly reduced by oleic acid compared with saline at all time points (Fig. 4*A*; all *P* values < 0.05), and the suppression was significantly greater than the load at 3, 6, and 23 h [Fig. 4*B*; t'(6) = 3.05, 4.57, and 4.32, respectively; all *P* values < 0.025]. The difference in weight gain on oleic acid (-4.0 ± 3.1 g) and saline (2.7 ± 1.1 g) tests was significant [t(6) = 2.57, P < 0.025].

Experiment 2. Mean suppression of intake produced by jejunal linoleic acid at 0.1 ml/h for 7 h (0.014 kcal/min) was approximately equal to calories infused (Fig. 5). Intake was not significantly different at any time point on lipid- and saline-infusion tests (all *P* values > 0.40). Similarly, there was no reliable difference in 4-day weight gain between tests with linoleic acid (2.3 ± 2.2 g) or saline [7.0 ± 2.9 g; t(9) = 1.42, P > 0.05].

By contrast, when the same load of linoleic acid was delivered at 0.2 ml/h (0.027 kcal/min) for 3.5 h, effects on intake and body weight were similar to those produced by twice the load in *experiment 1*. As in that study, ANOVA suggested that the effect of linoleic acid



Fig. 4. *A*: cumulative intake 1, 3, 6, and 23 h after food presentation in rats (n = 7) receiving jejunal infusions of oleic acid or saline at 0.2 ml/h for 7 h on 4 consecutive days. Values shown are means pooling across days. *P < 0.05 and **P < 0.01 for comparison of oleic acid and saline tests. *B*: mean differences in intake (±SE) between saline and oleic acid tests (solid line) compared with load delivered (dashed line). *P < 0.05 for comparison of mean suppression vs. load.



Fig. 5. *A*: cumulative intake in rats (n = 10) receiving jejunal infusions of linoleic acid or saline at 0.1 ml/h for 7 h on 4 consecutive days. Values shown are 4-day means. *B*: mean differences (\pm SE) between saline and linoleic acid tests (solid line) in relation to load delivered (dashed line).

infusion was consistent across days (*P* values for the infusate × days and infusate × days × time interactions > 0.20), so Fig. 6 shows means for cumulative intake pooled over days. Intake was significantly reduced by linoleic acid compared with saline at all sampling intervals [t'(8) = 3.74, 6.08, 9.60, and 8.15 for 1, 3, 6, and 23 h, respectively; all *P* values < 0.005]. Suppression was significantly greater than the infused load (5.7 kcal) at 3, 6, and 23 h [t'(8) = 3.40, 7.03, and 5.71, respectively; all *P* values < 0.01]. Total caloric intake averaged 75.6 kcal/day compared with 89.1 kcal/day on tests with saline infusion. Linoleic acid significantly suppressed 4-day weight gain [0.9 ± 1.0 vs. 5.6 ± 1.4 g; t(8) = 3.35, *P* < 0.01].

Experiment 3. Linoleic acid infusions at 0.2 ml/h for 7 h/day (11.5 kcal/day) on 21 consecutive days produced consistent decreases in intake and substantial reductions in body weight and fat relative to controls. A three-factor (day × time × group) ANOVA yielded nonsignificant day × group and day × time × group interactions (*P*values > 0.05), suggesting that suppression of intake produced by linoleic acid did not vary across days (see Fig. 7 for 23-h results). Mean 6- and 23-h intakes pooling over days are shown in Fig. 8. Intake of liquid diet was significantly lower at both times in the group receiving linoleic acid [t'(12) = 5.62 and 6.78, respectively; *P*values < 0.001]. Furthermore, suppression was greater than load at both 6 and 23 h [t'(12) = 3.86 and 3.87, respectively; *P*values < 0.005].



Fig. 6. *A*: cumulative intake in rats (n = 9) receiving jejunal infusions of linoleic acid or saline at 0.2 ml/h for 3.5 h on 4 consecutive days. Values shown are means pooling across days. **P < 0.01 for comparison of linoleic acid and saline tests. *B*: mean differences (\pm SE) in intake between saline and linoleic acid tests compared with load delivered (dashed line). **P < 0.01 for comparison of mean suppression vs. load.

Mean total caloric intake across 21 days was 80.8 kcal/day kcal (69.3 kcal/day ingested plus 11.5 kcal infused) for the linoleic acid group, a reduction of 16% compared with controls (96.1 kcal/day). The 95% confi-



Fig. 7. Mean 23-h food intake for rats receiving jejunal infusions (0.2 ml/h for 7 h) of linoleic acid (n = 6) or saline (n = 8) on 21 consecutive days (*days 1–21*). Graph shows daily means beginning day before onset of lipid infusions (*day 0*) with SE shown for every 3rd day. Total intake for linoleic acid (LA) group equals consumption plus load.



Fig. 8. A: cumulative intake in rats receiving linoleic acid or saline at 0.2 ml/h for 7 h on 21 consecutive days. Values shown are means for 6 and 23 h pooling across days. **P < 0.01 for comparison of linoleic acid and saline tests. B: mean differences (±SE) in intake between saline and linoleic acid groups (solid line) compared with load (dashed line). **P < 0.01 for comparison of mean suppression vs. load.

dence interval for the difference in total intake between the groups ranged from 6.7 to 23.9 kcal/day. As in the previous experiments, linoleic acid blocked the weight gain shown by rats receiving saline (Fig. 9). On *day 21*,



Fig. 9. Mean body weights of groups receiving jejunal infusions of linoleic acid or saline on 21 consecutive days beginning 5 days before onset of lipid infusions. SE shown for every 3rd day. **P < 0.01 for comparison of means in 2 groups on last day of experiment.

mean body weight was reduced by 10% in the linoleic acid group (445.2 \pm 11.8 g) compared with controls [492.1 \pm 10.3 g; *t*(12) = 3.00, *P* < 0.01].

Rats in the lipid-infusion group exhibited a 48% reduction in carcass fat relative to controls [t(12) = 3.15, P < 0.01] accompanied by a small (7%) but significant [t(12) = 3.03, P < 0.025] decrease in FFDM (Fig. 10).

DISCUSSION

These studies have shown that infusions of free fatty acids (linoleic and oleic acid) into the midjejunum produce significant rate-dependent reductions in food intake with concomitant decreases in body weight and carcass fat. In three experiments, slow fatty acid infusions (0.2 ml/h; 0.027 kcal/min) on 4 or 21 consecutive days produced decreases in daily food intake well in excess of the load. It is noteworthy that the amount of cumulative suppression was sustained in the interval between termination of infusions at 2.5 or 6 h after food presentation and the final measurement of food intake at 23 h; there was no compensation for the suppression occurring during the infusions. The observed effects were rate dependent because reducing the infusion rate from 0.027 to 0.014 kcal/min eliminated the suppression. On the other hand, when delivered at a greater rate of 0.027 kcal/min, a load as small as 5.7 kcal ($\sim 6\%$ of baseline intake) resulted in total caloric intake 15% lower than on control tests. In the third experiment, food intake remained suppressed to a similar extent throughout the 21-day regimen. The normal weight gain exhibited by rats on a highly palatable liquid diet was effectively eliminated by 0.027 kcal/min fatty acid infusions in all three experiments, and in the final study carcass fat was reduced by almost half in the treatment group.

In studies performing acute tests, other authors have reported that lipid infusions into the duodenum in rats (16, 25) and jejunum in human subjects (23) suppressed intake in excess of caloric load. In multiple-day studies



Fig. 10. Mean carcass content (\pm SE) of water, ether-extractable lipids, and fat-free dry mass (FFDM) of groups receiving jejunal infusions of linoleic acid or saline on 21 consecutive days. *P < 0.05 and **P < 0.01 for comparisons between groups.

on rats, similar effects on intake were reported by Glick and Modan (7) and Burton-Freeman and Schneeman (3). The former authors infused soybean oil continuously into the duodenum or ileum for 3-8 days and found infusions at these two sites to be equally effective in suppressing intake. They found, however, that the rate of weight gain was similar before and during these infusions, possibly because the observed reduction in intake was somewhat less than what we found. Burton-Freeman and Schneeman (3) infused 10% Intralipid into the duodenum for 3.8 h/day for 14 days and found suppression of both total intake and weight gain. It is worth noting, however, that infusion rates in the latter study were much higher than those used here. Even their slower rate (0.14 kcal/min) was more than five times the effective rate used in the current experiments (0.027 kcal/min). Their total load (33 kcal) was approximately one-half of the baseline intake and three times the largest load used here. Our results show that intestinal fatty acid infusions can produce suppression of total intake, body weight, and body fat even when the infusion rate is within the estimated physiological range for gastric emptying of lipids (6, 10, 14) and the load is only a small percentage of total intake.

The ability of such slow infusions to reduce intake with relatively short latency (1-h measurement) is consistent with hypothesized satiety mechanisms stimulated by lipids within the small intestine (8, 9). Admittedly, the existence of such mechanisms is controversial. Friedman and colleagues (6, 10) have argued that many previous demonstrations of suppression of intake by intestinal lipid infusions have used 1) infusion rates that were excessive (>0.1 kcal/min) relative to gastric emptying in rats (6, 10) and 2) infusates producing damage within the intestine (19). With regard to the first point, several recent studies on rats have estimated gastric emptying rate of lipid loads to be 0.08 kcal/min or less (6, 10, 14). In this sense, our effective rate of 0.027 kcal/min can be considered physiological. In two reports describing effects of duodenal infusions of emulsified oleic acid in rats, Reidelberger and colleagues (24, 25) have observed rate dependence similar to our results, with a minimum effective rate for suppressing 4-h cumulative intake of ~ 0.03 kcal/min. Thus a supraphysiological rate of infusion is not necessary for suppression of intake. It is also worth noting that we did not observe diarrhea, although it has been found to result from intestinal administration of lipids at higher rates than we used here (16). Concerning the second point above, lipid formulations with potent surfactant action, particularly sodium oleate and to a lesser extent Intralipid, may injure the wall of the intestine as indicated by increased activity of lactate dehydrogenase (19). However, free oleic acid was tested in the same study and did not produce evidence of damage. Thus, whereas we did not directly address the possibility that our infusions reduced intake because they were aversive, our use of low infusion rates and our avoidance of infusates known to produce intestinal damage make this possibility less likely.

It is likely that a preabsorptive satiating action of fatty acids within the jejunum involves stimulation of vagal afferents within the celiac branches, which provides the bulk of the vagal innervation of the distal small intestine (1, 17). Severing these fibers has been reported to abolish the acute effect of intraintestinal oleic acid on food intake (22). We have shown that infusions of linoleic acid into the jejunum or ileum increase multiunit activity of celiac vagal afferents in rats (20), consistent with an earlier report of increased vagal activity in response to intraintestinal lipids in cats (15). Little information is available regarding the nature of the signaling pathway giving rise to increased afferent activity. However, we found that the vagal response to ileal administration of linoleic acid is blocked by prior treatment with Pluronic L-81, suggesting that chylomicron formation is a necessary step in the pathway (20). Parenthetically, recordings were made from celiac afferents in the rats used in experi*ment 3* after completion of the behavioral study. In tests involving jejunal administration of 1 ml of linoleic acid, animals that had received linoleic acid on 21 consecutive days showed no sign of desensitization compared with the group previously receiving saline (data not shown). If there is a vagal contribution to the behavioral effects of linoleic acid infusions, then this persistence of vagal responsiveness is consistent with our observation of continuing suppression of intake with repeated administration of fatty acids and differs from the reported diminished effectiveness of intestinal lipid infusions for slowing intestinal transit after repeated exposure (2).

Although suppression of consumption per se occurred within the first hour of food availability, it is noteworthy that suppression of total intake occurred with longer latency. In three sets of tests involving infusion of linoleic (Figs. 2 and 6) or oleic (Fig. 4) acid at 0.2 ml/h, suppression at the 1-h measurement was approximately equal to the load delivered by that time (3.3 kcal); median ratios of suppression to load ranged from 1.1 to 1.3. By contrast, suppression was substantially and significantly greater than load (6.6 kcal) after access to food for 3 h, and median suppression ratios ranged from 2.1 to 2.7 in those three tests. We speculate that this long-latency overcompensation reflects the mobilization of a second mechanism. Its time course is consistent with postabsorptive action of the infused fatty acids, possibly involving changes in hepatic lipid metabolism (5, 10, 13). Such postabsorptive action might also account for the lack of compensatory overeating in the intervals between infusions.

In summary, slow jejunal delivery of two fatty acids reduced food intake, body weight, and carcass fat in multiple-day experiments. Infused caloric loads as small as 6% of baseline intake were effective when delivered at 0.027 kcal/min, a rate slower than published estimates of gastric emptying of fat loads (6, 10, 14). Suppressive effects of the load were persistent in two senses, both of which were critical for the observed cumulative effects on energy balance. First, there was little or no feeding rebound in the 17- or 20.5-h interval between the end of one day's infusion and the beginning of the next day's. Second, effects were persistent in the sense that we saw no evidence of their diminution, neither loss of feeding suppression nor recovery of body weight, when infusions were given for 21 days. These results appear to reflect the activation of both pre- and postabsorptive mechanisms, but more research is required before firm conclusions can be drawn. Finally, our results suggest a promising approach to the treatment of human obesity, involving calorically trivial loads of fatty acids delivered orally but targeting the jejunum.

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