

# Central Administration of Oleic Acid Inhibits Glucose Production and Food Intake

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The hypothalamus and other regions within the central nervous system (CNS) link the sensing of nutrients to the control of metabolism and feeding behavior. Here, we report that intracerebroventricular (ICV) administration of the long-chain fatty acid oleic acid markedly inhibits glucose production and food intake. The anorectic effect of oleic acid was independent of leptin and was accompanied by a decrease in the hypothalamic expression of neuropeptide Y. The short-chain fatty acid octanoic acid failed to reproduce the metabolic effects of oleic acid, and ICV coadministration of inhibitors of ATP-sensitive  $K^+$  channels blunted the effect of oleic acid on glucose production. This is the first demonstration that fatty acids can signal nutrient availability to the CNS, which in turn limits further delivery of nutrients to the circulation. *Diabetes* 51:271–275, 2002

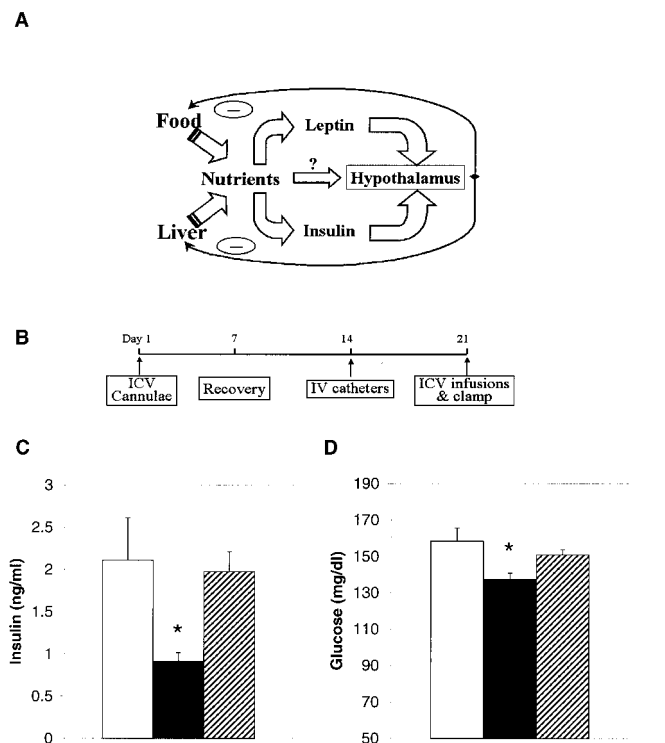
Excessive consumption of nutrients with high caloric density is largely responsible for the epidemic of obesity and type 2 diabetes in the western hemisphere and in developing nations (1,2). The association of nutrient excess and obesity with type 2 diabetes is largely mediated via their negative impact on intermediary metabolism and insulin action (1–3). Control of metabolism and food intake in response to nutrients occurs partly at the level of hypothalamic nuclei (3–5). In this regard, macronutrients, such as carbohydrates and lipids, regulate the circulating levels of leptin and insulin (3,6,7), which in turn modulate appetite, energy expenditure, and intermediary metabolism mainly via their hypothalamic receptors (Fig. 1A) (3–5). However, central nervous system (CNS) neurons may also sense nutrients directly via metabolic signaling (8). In this regard, the potential role of CNS lipid metabolism in the control of appetite is supported by the potent anorectic property of fatty acid synthase inhibitors (9,10). Further-

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Received for publication 3 October 2001 and accepted in revised form 26 November 2001. Posted on the World Wide Web at [http://www.diabetes.org/diabetes\\_rapids](http://www.diabetes.org/diabetes_rapids) on 20 December 2001.

aCSF, artificial cerebral spinal fluid; CNS, central nervous system; FFA, free fatty acid; GIR, glucose infusion rate; HBP, hydroxypropyl- $\beta$ -cyclodextrin; ICV, intracerebroventricular;  $K_{ATP}$ , ATP-sensitive  $K^+$  channel; LC-CoA, long-chain fatty acyl CoA; NPY, neuropeptide Y.



**FIG. 1.** Rapid effects of ICV oleic acid on plasma insulin and glucose levels. **A:** Hypothesis on the negative feedback mechanisms regulating circulating nutrients. There are two main sources of circulating nutrients: intake and absorption of food (Food) and hepatic production of glucose and lipids (Liver). Increased levels of plasma glucose and lipids regulate hypothalamic efferent pathways via their stimulatory effects on insulin and leptin biosynthesis and secretion. The activation of these central responses leads to decreases in food intake and in hepatic output of glucose and lipids. It is proposed herein that circulating nutrients may also directly signal the nutritional status to the hypothalamus and may therefore play a role in this feedback system. **B:** Schematic representation of the experimental procedures. Surgical implantation of ICV cannulae was performed on day 1 (~3 weeks before the in vivo study). Full recovery of body weight and food intake was achieved by day 7. Surgical implantation of IV catheters was performed on day 14. Finally, on day 21, ICV infusions were started and blood chemistries, food intake, and/or insulin action were assessed. **C:** ICV oleic acid markedly decreased circulating insulin levels. The effects of ICV oleic acid (■) on plasma insulin concentrations (average of at least four measurements between 2 and 4 h after the start of the ICV infusion) was compared with that of ICV vehicle (□) and ICV octanoic acid (▨). At 2 h from the start of the ICV infusion, oleic acid markedly decreased plasma insulin concentrations compared with either control group ( $P < 0.01$ ). **D:** ICV oleic acid decreased circulating glucose levels. The effects of ICV oleic acid (■) on plasma glucose concentrations (average of at least five measurements between 2 and 4 h after start of the ICV infusion) is compared with that of ICV vehicle (□) and octanoic acid (▨). At 2 h from the start of the ICV infusion, oleic acid significantly decreased plasma glucose concentrations compared with either control group ( $P < 0.05$ ).

TABLE 1  
General characteristics of the experimental groups before the ICV infusions and during the insulin clamp studies

	Vehicle	Oleic acid	Octanoic acid	Sulfonylurea	Oleic acid sulfonylurea
<b>Basal</b>					
<i>n</i>	14	21	5	6	6
Body weight (g)	325 ± 7	317 ± 5	330 ± 12	325 ± 11	317 ± 7
Glucose (mmol/l)	8.3 ± 1.0	8.1 ± 0.7	8.2 ± 1.0	8.1 ± 0.8	8.0 ± 0.9
Insulin (ng/ml)	1.6 ± 0.2	1.4 ± 0.2	1.8 ± 0.3	1.9 ± 0.3	1.4 ± 0.3
FFA (mmol/l)	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.2
Leptin (ng/ml)	1.4 ± 0.2	1.1 ± 0.1	1.2 ± 0.1	1.5 ± 0.2	1.3 ± 0.2
<b>Clamp</b>					
<i>n</i>	5	10	5	6	6
Glucose (mmol/l)	8.0 ± 1.0	8.0 ± 0.7	8.2 ± 1.0	8.1 ± 0.8	7.9 ± 0.8
Insulin (μU/ml)	16 ± 2	17 ± 3	17 ± 3	18 ± 2	16 ± 3
FFA (mmol/l)	0.5 ± 0.1	0.5 ± 0.1	0.6 ± 0.2	0.6 ± 0.1	0.4 ± 0.1
Leptin (ng/ml)	1.3 ± 0.1	0.9 ± 0.2	1.1 ± 0.1	1.5 ± 0.2	1.3 ± 0.1

Data are means ± SE. The values during the clamp represent steady-state levels obtained by averaging at least five plasma samples during the experimental period.

more, long-chain fatty acyl CoAs (LC-CoAs), such as oleylCoA, can activate ATP-sensitive K<sup>+</sup> (K<sub>ATP</sub>) channels in nonneuronal cells (11,12). Of interest, some of the more rapid hypothalamic effects of leptin and insulin may also be mediated via the activation of K<sub>ATP</sub> channels in selective neurons (13–15).

Circulating fatty acids gain rapid access to the brain, where they equilibrate with neuronal LC-CoAs (16,17). They are then further metabolized via mitochondria β-oxidation or incorporated into phospholipids (16,17). Here, we hypothesize that fatty acids may signal nutritional status to selective CNS neurons and activate a feedback loop designed to curtail further input of nutrients into the circulation. To investigate the central effects of fatty acids independent of their pleiotropic peripheral actions, we examined whether the administration of oleic acid in the third cerebral ventricle acutely regulates insulin action and food intake (Fig. 1A).

## RESEARCH DESIGN AND METHODS

We studied 52 10-week-old male Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, MA). Rats were housed in individual cages and subjected to a standard light-dark cycle (0600–1800/1800–0600). At 3 weeks before the *in vivo* studies, we placed a chronic catheter in the third cerebral ventricle by stereotaxic surgery (18). Rats were anesthetized with intraperitoneal ketamine (Ketaset, 87 mg/kg) and xylazine (Rompun, 11 mg/kg) and fixed in a stereotaxic apparatus with ear bars and a nose piece set at +5.0 mm. A 26-gauge stainless steel–guide cannula (Plastics One, Roanoke, VA) was chronically implanted into the third ventricle, using the following coordinates from Bregma: anterior-posterior; +0.2 mm dorsal-ventral; –9.0 mm medial-lateral; 0.0 directly on the midsagittal suture. At 1 week before all experimental protocols, we placed additional catheters in the right internal jugular and left carotid artery (18–21). All intracerebroventricular (ICV) solutions were dissolved in artificial cerebral spinal fluid (aCSF). To safely deliver fatty acids in a cerebral ventricle, they were complexed with the polymer hydroxypropyl-β-cyclodextrin (HBP) (22,23), which was purchased from CTD. HBP was also included in all other ICV solutions. The metabolic and feeding experiments were performed ~3 weeks after stereotaxic surgery, after complete recovery from the operation (Fig. 1B). We first examined three groups of conscious rats receiving an ICV infusion of oleic acid (*n* = 10), octanoic acid (*n* = 5), or vehicle (*n* = 5) (Table 1). Octanoic acid was included to compare the effects of a long-chain fatty acid (oleic acid) with that of a short-chain fatty acid.

The infusion studies lasted a total of 360 min (Fig. 2A). At *t* = 0, a primed-continuous ICV infusion of oleic acid (total dose 30 nmol), vehicle (HBP 10% in aCSF), or octanoic acid (total dose 30 nmol) was initiated and maintained for the remainder of the study. At *t* = 120, an infusion of labeled glucose (40 μCi bolus of high-performance liquid chromatography–purified [<sup>3</sup>H-3]glucose; New England Nuclear, Boston, MA) was initiated and maintained for the last 4 h of the study. Finally, pancreatic-insulin clamp study was

initiated at *t* = 240 min and lasted for 2 h. This procedure involved the infusion of somatostatin (3 μg · kg<sup>-1</sup> · min<sup>-1</sup>), insulin (1 mU · kg<sup>-1</sup> · min<sup>-1</sup>), and glucose as needed to prevent hypoglycemia. The rate of insulin infusion was designed to replace normal basal levels in postabsorptive rats.

We next examined three groups of conscious rats receiving an ICV infusion of one of the following: a sulfonylurea (tolbutamide or glybenclamide, *n* = 6), oleic acid, or oleic acid (total dose 30 nmol) plus a sulfonylurea (*n* = 6) (Table 1). At *t* = 0, a primed-continuous ICV infusion of tolbutamide (30 nmol), glybenclamide (3 nmol), oleic acid (total dose 30 nmol), or oleic acid (total dose 30 nmol) plus either tolbutamide (30 nmol) or glybenclamide (3 nmol) was initiated and maintained for the 6-h-long study. The pancreatic-insulin clamp procedure was performed as described above. The plasma insulin and glucose concentrations displayed in Fig. 1C and D represent the averages of at least four samples obtained between 120 and 240 min.

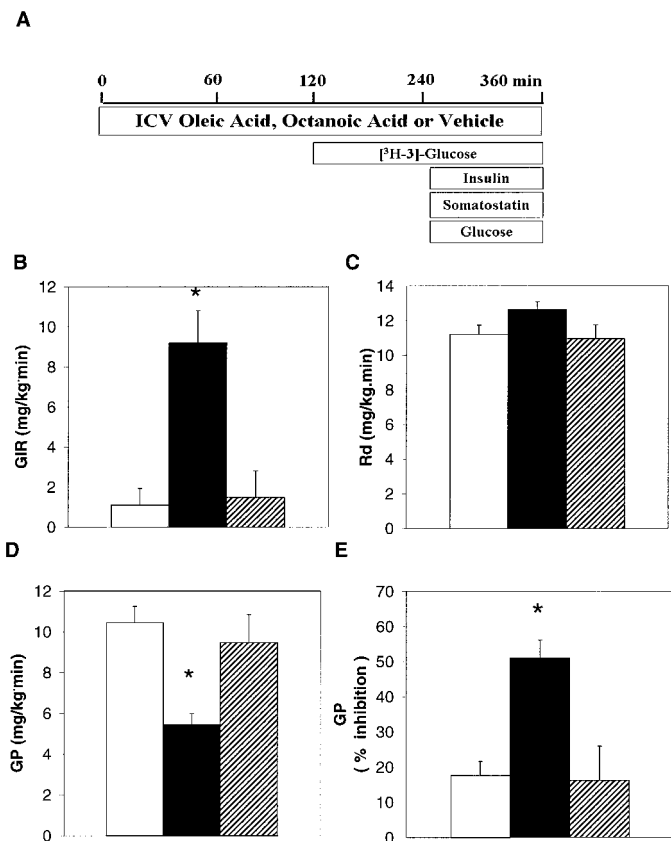
Finally, we examined the effect of ICV oleic acid on food intake. At 1 h before the start of the dark cycle, oleic acid (30 nmol in 3 μl, *n* = 11) or vehicle (HBP 10% in aCSF, *n* = 9) were injected as a bolus via indwelling catheters implanted in the third cerebral ventricle. Rats were adapted to the metabolic cages, and their daily food intake had been constant (changes <10%) for a minimum of 3 consecutive days preceding the ICV injections.

Additional experiments designed to examine the effect of ICV oleic acid per se on the hypothalamic expression of neuropeptide Y (NPY), vehicle (*n* = 5), or oleic acid (*n* = 5) were also injected ICV 1 h before the start of the dark cycle. However, food was withdrawn overnight, and hypothalami were rapidly harvested the following morning. Hypothalamic RNA was analyzed by Northern blot using full-length probes for prepro-NPY and β-actin (the latter was used as a control for RNA quantification). Probes were labeled with <sup>32</sup>P using a random primer kit (Stratagene).

All values are presented as the means ± SE. Comparisons among groups were made using repeated measures analysis of variance (clamp studies) and unpaired Student's *t* test (food intake studies). The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee of the Albert Einstein College of Medicine.

## RESULTS

The infusion of oleic acid in the third cerebral ventricle resulted in a marked decline in the plasma insulin concentration (0.9 ± 0.1 vs. 2.1 ± 0.4 ng/ml) and a modest decrease in the plasma glucose concentration (139 ± 2 vs. 152 ± 3 mg/dl) compared with ICV vehicle (Fig. 1C and D). These changes were detectable within 1 h from the start of the infusion and suggested that ICV oleic acid may enhance insulin sensitivity. Thus, insulin action was assessed by a combination of ICV infusions and systemic pancreatic-insulin clamp studies (Fig. 2A). As expected in the presence of near basal circulating insulin levels (clamp procedure) (Table 1), the glucose infusion rate (GIR) required to maintain euglycemia was marginal in ICV vehicle–infused animals (1.1 ± 0.8 mg · kg<sup>-1</sup> · min<sup>-1</sup>). In



**FIG. 2.** ICV oleic acid enhances insulin action and inhibits glucose production. **A:** Schematic representation of the pancreatic-insulin clamp procedures. The infusion studies lasted a total of 360 min. ICV infusions were initiated at  $t = 0$  and maintained for the remainder of the study. At  $t = 120$ , an infusion of labeled glucose was initiated and maintained for the last 4 h of the study. Finally, the pancreatic-insulin clamp study was initiated at  $t = 240$  min and lasted for 2 h. **B:** Effect of ICV oleic acid (■) on GIR. In the presence of near basal insulin concentrations, there was virtually no need to infuse exogenous glucose during ICV vehicle (□) and ICV octanoic acid (▨). However, infusion of exogenous glucose at a rate of  $>9 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  was required to prevent hypoglycemia during ICV oleic acid infusion. **C:** Effect of ICV oleic acid on the rate of glucose disappearance ( $R_d$ ).  $R_d$  was not significantly affected by ICV oleic acid compared with both control groups. **D:** Effect of ICV oleic acid on the rate of glucose production (GP). The rates of glucose production were similar in all experimental groups before start of the pancreatic-insulin clamp ( $12.1 \pm 0.4$ ,  $11.4 \pm 0.4$ , and  $11.3 \pm 0.8 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  in ICV vehicle, oleic acid, and octanoic acid, respectively). In the presence of near basal insulin concentrations, ICV oleic acid markedly inhibited the rate of glucose production compared with ICV vehicle ( $P < 0.01$ ) and ICV octanoic acid ( $P < 0.01$ ). **E:** Effect of ICV oleic acid on the percent decline in glucose production during the clamp procedure. In rats receiving ICV oleic acid, the rate of glucose production was markedly decreased (by 51%) during the clamp procedure compared with basal measurement.

contrast, after ICV oleic acid, glucose had to be infused at a rate of  $9.2 \pm 1.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  to prevent hypoglycemia (Fig. 2B). Finally, ICV administration of equimolar amounts of octanoic acid failed to alter GIR ( $1.5 \pm 1.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) during the clamp procedure. Thus, central administration of a long-chain fatty acid, but not of a short-chain fatty acid, decreases systemic insulin levels and, in the presence of fixed and basal insulin concentrations, markedly stimulates insulin action on glucose homeostasis.

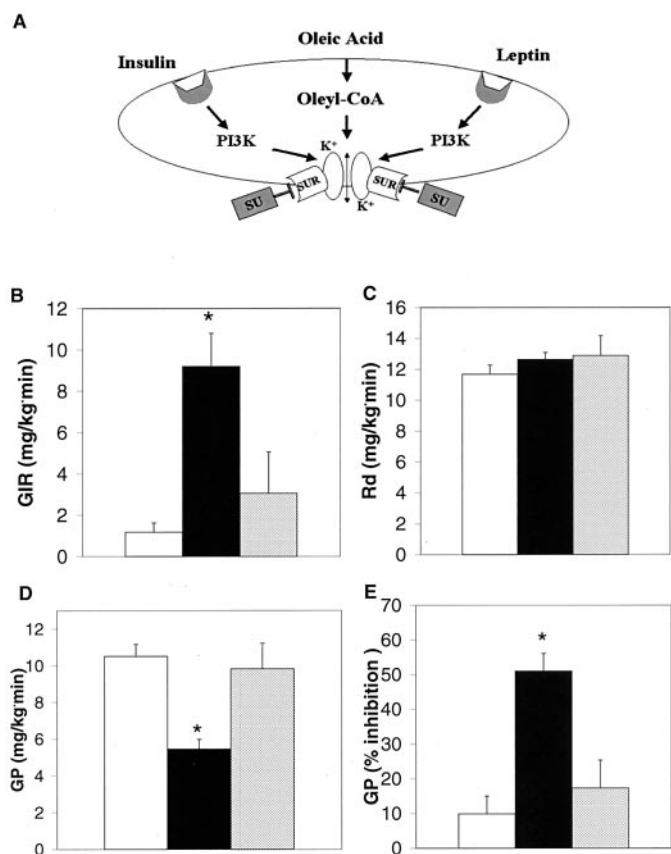
We next examined the potential mechanism(s) by which ICV oleic acid lowers plasma insulin and glucose levels and enhances whole-body insulin action. We assessed

glucose kinetics by tracer dilution methodology (18,20,21) to establish whether the increased GIR induced by ICV oleic acid was caused by stimulation of glucose uptake or by suppression of endogenous glucose production. The rate of glucose uptake was not significantly affected by oleic acid (Fig. 2C). Conversely, ICV oleic acid markedly suppressed the rate of glucose production (to  $5.4 \pm 0.7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) compared with both control groups ( $10.5 \pm 0.8$  and  $10.1 \pm 1.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  in ICV vehicle and octanoic acid, respectively) (Fig. 2D). ICV vehicle and ICV octanoic acid were associated with modest ( $\sim 16\%$ ) declines in the rate of glucose production from basal levels, probably reflecting the gradual transition toward fasting. However, ICV oleic acid led to a marked ( $51 \pm 5\%$ ) decline in the rate of glucose production compared with basal levels (Fig. 2E). This decrease in glucose output occurred in the presence of similar and low plasma insulin levels ( $\sim 16 \mu\text{U/ml}$ ) (Table 1), and it largely accounted for the effect of ICV oleic acid on whole-body glucose metabolism.

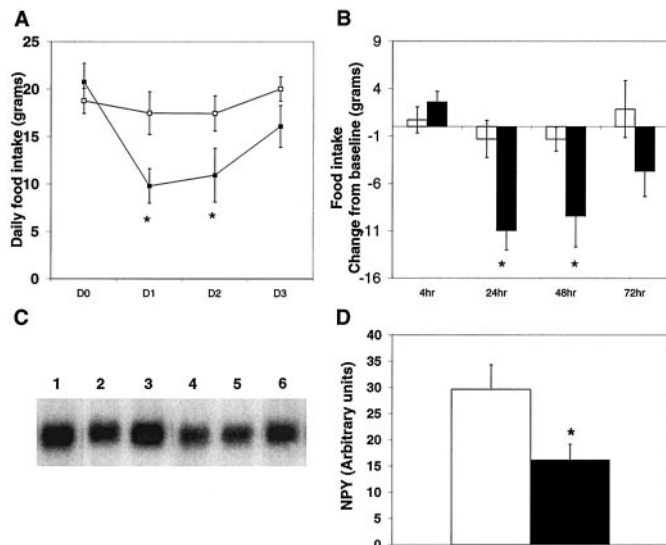
Because  $K_{\text{ATP}}$  channels are expressed in the hypothalamus (13,15) and LC-CoAs can activate  $K_{\text{ATP}}$  channels in some cell systems (11,12), we next asked whether the potent and rapid effects of ICV oleic acid on glucose production required activation of hypothalamic  $K_{\text{ATP}}$  channels. Sulfonylureas are potent inhibitors of  $K_{\text{ATP}}$  channels, and they block the activation of hypothalamic  $K_{\text{ATP}}$  channels by insulin and leptin (13,15). Thus, the coadministration of a sulfonylurea with oleic acid is expected to prevent hypothalamic  $K_{\text{ATP}}$  channel activation by oleic acid (Fig. 3A). Importantly, in the presence of basal insulin levels (Table 1), the ICV infusion of sulfonylurea alone (either tolbutamide or glybenclamide) failed to affect GIR ( $1.2 \pm 0.5$ ) or glucose production ( $10.5 \pm 0.7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) compared with ICV vehicle. When either sulfonylurea was coinjected, ICV oleic acid failed to regulate GIR ( $3.0 \pm 1.9$ ) (Fig. 3B) and rates of glucose production ( $9.8 \pm 1.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) (Fig. 3C and D). Thus, ICV administration of inhibitors of  $K_{\text{ATP}}$  channels blunts the potent metabolic effects of ICV oleic acid. This experiment suggests that oleic acid acutely enhances hepatic insulin action via the activation of  $K_{\text{ATP}}$  channels in the hypothalamus and/or in other CNS areas affected by our ICV infusions. In this regard, ICV administration of leptin and insulin has also been shown to exert rapid effects on the regulation of hepatic glucose fluxes (18,24). It is likely that these rapid metabolic effects of oleic acid, insulin, and leptin may involve activation of  $K_{\text{ATP}}$  channels in selective CNS neurons (Fig. 3A) (11,12,24).

Thus, oleic acid appears to mimic selective actions of two centrally active anorectic hormones, leptin and insulin. Furthermore, inhibition of fatty acid synthase markedly reduces food intake (9,10). The anorectic effects of inhibitors of fatty acid synthase require an increase in the concentration of malonylCoA in selective neurons (9). Because malonylCoA is a potent inhibitor of the entry of LC-CoAs into the mitochondria via inhibition of the activity of the enzyme carnitine palmitoyl-transferase-1 (25,26), we hypothesized that an elevation in neuronal LC-CoAs could mediate the anorectic effect of fatty acid synthase inhibitors.

Based on these previous findings (9,11,12,25,26), we



next examined whether ICV oleic acid modulates feeding behavior and hypothalamic NPY expression in conscious rats. To this end, 1 h before the onset of the dark cycle, two groups of rats received a bolus of either vehicle or oleic acid via an indwelling ICV catheter. Food intake was



monitored in metabolic cages before and after the ICV injections. ICV oleic acid induced a marked decrease in food intake compared with baseline and vehicle (Fig. 4A). Vehicle did not significantly alter food intake at any time after its ICV administration. Conversely, the changes from baseline induced by oleic acid were statistically significant at 24 ( $-11 \pm 2$  g) and 48 h ( $-9 \pm 3$  g) after its ICV administration (Fig. 4B). This represented a 52 and 44% decrease in daily food intake, respectively, which returned to baseline values by 72 h. To examine the effect of ICV oleic acid per se on hypothalamic NPY mRNA, we performed Northern blot analysis 12 h after a single ICV injection of either oleic acid or vehicle in fasted rats. ICV oleic acid decreased the hypothalamic expression of NPY (Fig. 4C and D). These data support the notion that long-chain fatty acids may directly control food intake via their action on hypothalamic centers. Furthermore, increases in LC-CoA levels in selective neurons within the hypothalamus or in other regions of the CNS are likely to account for the potent effects of inhibitors of fatty acid synthase on food intake and NPY mRNA (9).

**DISCUSSION**

Based on these results, we conclude that the long-chain fatty acid oleic acid has potent effects on hypothalamic neurons and likely on other CNS neurons. Taken together with recent studies on the metabolic actions of leptin and melanocortins (18,27), the present findings support the notion that common central pathways are involved in the

regulation of both energy homeostasis and hepatic insulin action. Because glucose production by the liver is the major source of endogenous fuel, central neural circuitries concomitantly modulate exogenous and endogenous sources of energy. This is consistent with a negative feedback system designed to monitor and regulate the input of nutrients in the circulation (Fig. 1A). Finally, the activation of CNS  $K_{ATP}$  channels is required for the rapid actions of ICV oleic acid on plasma insulin and glucose levels and on glucose production. The latter observation adds support to the notion that excitability of selective neurons within the hypothalamus or in other areas within the CNS is blunted by leptin (13), insulin (15), and fatty acids via activation of  $K_{ATP}$  channels, leading to cellular hyperpolarization. However, it should be noted that the effects of ICV oleic acid on food intake were not detectable during the first 4 h after its injection. Furthermore, we did not examine the effects of ICV octanoic acid and ICV sulfonylureas on food intake. Thus, it is possible that distinct mechanisms account for the metabolic and behavioral actions of oleic acid in the CNS. In particular, the effects on food intake may require regulation at the transcriptional level and/or diffusion of the fatty acid in more remote regions of the CNS. Furthermore, there is scarce information on the concentration of free fatty acids (FFAs) in the cerebral spinal fluid. In fasted anesthetized dog cerebral spinal fluid, FFA levels were estimated at  $\sim 25 \mu\text{mol/l}$  (or  $\sim 6\%$ ) of the concentration in plasma (28). Because we do not know the volume of distribution of the ICV oleic acid (total dose 30 nmol) in the present study, it is difficult to draw conclusions on the increase in cerebral spinal fluid FFA levels induced with this procedure. Overall, considering that circulating FFAs can gain rapid access to the CNS (16,17), it is likely that these potent behavioral and metabolic effects of oleic acid play an important role in the regulation of energy balance and insulin action.

Thus, the long-chain fatty acid oleic acid provides a signal of "nutrient abundance" to discrete areas within the CNS. This signal in turn activates a chain of neuronal events apparently designed to promote a switch in fuel sources from carbohydrates to lipids and to limit the further entry of exogenous and endogenous nutrients in the circulation. This restraint may be required for the maintenance of energy and metabolic homeostasis, and its failure could contribute to weight gain and glucose intolerance. The unveiling of this nutrient-activated neuronal circuitry may lead to innovative approaches to the treatment of obesity and type 2 diabetes.

#### ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (DK-48321 and DK-45024, to L.R.) and the AECOM Diabetes Research & Training Center (DK-20541). S.O. was the recipient of a postdoctoral fellowship from the American Diabetes Association.

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