A Functional Melanocortin System May Be Required for Chronic CNS-Mediated Antidiabetic and Cardiovascular Actions of Leptin

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OBJECTIVE—We recently showed that leptin has powerful central nervous system (CNS)-mediated antidiabetic and cardiovascular actions. This study tested whether the CNS melanocortin system mediates these actions of leptin in diabetic rats.

RESEARCH DESIGN AND METHODS—A cannula was placed in the lateral ventricle of Sprague-Dawley rats for intracerebroventricular infusions, and arterial and venous catheters were implanted to measure mean arterial pressure (MAP) and heart rate 24 h/day and for intravenous infusions. After recovery from surgery for 8 days, rats were injected with streptozotocin (STZ), and 5 days later, either saline or the melanocortin 3 and 4 receptor (MC3/4R) antagonist SHU-9119 (1 nmol/h) was infused intracerebroventricularly for 17 days. Seven days after starting the antagonist, leptin (0.62 μg/h) was added to the intracerebroventricular infusion for 10 days. Another group of diabetic rats was infused with the MC3/4R agonist MTII (10 ng/h i.c.v.) for 12 days, followed by 7 days at 50 ng/h.

RESULTS—Induction of diabetes caused hyperphagia, hyperglycemia, and decreases in heart rate (−76 bpm) and MAP (−7 mmHg). Leptin restored appetite, blood glucose, heart rate, and MAP back to pre-diabetic values in vehicle-treated rats, whereas it had no effect in SHU-9119–treated rats. MTII infusions transiently reduced blood glucose and raised heart rate and MAP, which returned to diabetic values 5–7 days after starting the infusion.

CONCLUSIONS—Although a functional melanocortin system is necessary for the CNS-mediated antidiabetic and cardiovascular actions of leptin, chronic MC3/4R activation is apparently not sufficient to mimic these actions of leptin that may involve interactions of multiple pathways. ***Diabetes*** **58:1749–1756, 2009**

Leptin, an adipocyte-derived peptide that circulates in proportion to the amount of body fat, is well known for its role in body weight homeostasis (1–3). Leptin informs the brain of the body's energy storage status and promotes weight loss by reducing appetite and increasing energy expenditure by stimulation of sympathetic nervous system activity to various tissues, including brown adipose tissue (4,5). In addition to its role in body weight homeostasis, leptin exerts important cardiovascular actions that are mediated via the central nervous system (CNS). For example, studies from our laboratory and others indicate that leptin may be an important link between excess weight gain and increased arterial pressure (6–9). Chronic hyperleptinemia in lean animals raises arterial pressure, whereas leptin deficiency causes severe obesity and many features of the metabolic syndrome without the accompanying hypertension (7–10).

Leptin also stimulates glucose utilization in peripheral tissues by activating CNS pathways. We recently showed that chronic intracerebroventricular infusion of leptin in diabetic rats completely restored blood glucose to normal levels and prevented the hyperphagia and the marked bradycardia associated with streptozotocin (STZ)-induced diabetes (11). These observations indicate that the powerful effects of leptin on glucose regulation and cardiovascular function in insulin-deficient diabetic rats are mediated, mainly by leptin's direct actions on the CNS, and are independent of insulin. However, the CNSs mechanisms that mediate leptin's chronic effects on glucose homeostasis and cardiovascular function are still unclear.

Leptin has been shown to suppress several orexigenic pathways including neuropeptide Y (NPY), agouti-related peptide (AGRP), and melanin-concentrating hormone, while activating anorexigenic pathways such as corticotrophin-releasing hormone, cocaine-amphetamine–related peptide, and the proopiomelanocortin (POMC) system (1–3,12–20). Among these factors, the POMC pathway appears to play a key role in mediating the appetite and cardiovascular CNS actions of leptin. Leptin-mediated stimulation of the POMC neurons leads to release of α-melanocyte stimulating hormone (α-MSH) and activation of the melanocortin 3 and 4 receptors (MC3/4R) in several brain nuclei (1,12). Activation of MC3/4R has been demonstrated to contribute importantly to the anorexic actions of leptin (13–15), while absence of functional melanocortin system, either by pharmacological blockade of the MC3/4R (9,16,17) or genetic disruption of the MC4R (18), results in complete unresponsiveness to the chronic blood pressure and heart rate effects of leptin. Acute and chronic studies also suggest that activation of the MC3/4R improves insulin sensitivity and that blockade of the MC3/4R causes marked insulin resistance (20–22). However, the role of the CNS melanocortin system in mediating the chronic antidiabetic and cardiovascular actions of leptin in insulin-deficient diabetes are still unknown.

In this study, we demonstrate that activation of the MC3/4R is required for leptin to exert its chronic antidiabetic and cardiovascular actions. Our results also indicate,

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however, that chronic stimulation of the MC3/4R alone, using a pharmacological agonist, causes only transient reductions in blood glucose in diabetic rats. These observations suggest that a functional melanocortin system is necessary for the CNS-mediated antidiabetic and cardiovascular actions of leptin, but chronic MC3/4R activation is apparently not sufficient to mimic these actions of leptin that may involve interactions of multiple pathways.

RESEARCH DESIGN AND METHODS

Animal surgeries. The experimental procedures and protocols of this study conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the University of Mississippi Medical Center.

Intra-arterial and intravenous catheterization. Male Sprague-Dawley (Harlan, Indianapolis, IN) rats (325–350 g, $n = 20$) were anesthetized with 50 mg/kg sodium pentobarbital (Nembutal), and atropine sulfate (0.1 mg/kg) was administered to prevent excess airway secretions. Arterial and venous catheters were implanted according to procedures previously described (11,22). Briefly, using aseptic techniques, a laparotomy was performed and a sterile nonocclusive polyvinyl catheter was inserted into the abdominal aorta, distal to the kidneys. Through a left femoral vein incision, a sterile catheter was placed in the vena cava. Both catheters were exteriorized through a subcutaneously implanted stainless steel button.

Intracerebroventricular cannulation. Immediately after arterial and venous catheter implantation, a stainless steel cannula (26 gauge, 10 mm long) was implanted into the right lateral cerebral ventricle using the coordinates previously described (22). The guide cannula was anchored into place with three stainless steel machine screws, a metal cap, and dental acrylic, and a stylet was inserted to seal the cannula until use. During stereotaxic manipulation, anesthesia was maintained with 0.5–1.5% isofluorane. After 7 days of recovery from surgery, accuracy of the cannula placement was tested by measuring the dipsogenic response (immediate drinking of at least 5 ml of water in 10 min) to an intracerebroventricular injection of 100 ng angiotensin II. After the experiment, the animals were killed and the brains removed and sectioned to confirm placement of the cannula.

After recovery from anesthesia, the rats were housed in individual metabolic cages for determination of daily water and food consumption. The arterial and venous catheters were connected to a dual-channel infusion swivel (Instech). The arterial catheter was connected to a pressure transducer (Maxxim) for continuous 24-h measurement of mean arterial pressure (MAP) and heart rate using computerized techniques as previously described (7,8). The venous catheter was connected to a syringe pump for continuous infusion of saline (0.45%, 40 ml/day). The rats received food and water ad libitum throughout the study. Total sodium intake was maintained constant at ~3.1 mEq/day via the continuous saline infusion combined with sodium-deficient rat chow (0.006 mmol sodium/g food, Teklad). Intravenous solutions were infused through a sterile filter (0.22 μm, Millipore), and the saline infusion was started immediately after placement of the rats into the metabolic cages. The rats were allowed to recover for 8–10 days before control measurements were initiated.

Experimental protocols. MAP, heart rate, urine volume, food, and water intake were measured 24 h/day and average values were recorded daily.

Induction of diabetes. After 4–5 days of stable control measurements, insulin-deficient diabetes was induced by a single intravenous injection of streptozotocin (STZ, 50 mg/kg [Sigma Aldrich], dissolved in 0.5 ml of 0.05 M citrate buffer, pH 4.5).

Chronic intracerebroventricular leptin infusion in diabetic rats ($n = 5$). Five days after STZ injection, leptin (0.62 μg/h, 0.5 μl/h) was infused intracerebroventricularly for 10 days via osmotic minipump (model 2002, Durect) implanted subcutaneously in the scapular region as previously described (20). We have shown that this rate of leptin infusion fully restores euglycemia in STZ-diabetic rats (11).

Chronic intracerebroventricular infusion of a MC3/4R agonist, MTII ($n = 10$). Five days after STZ injection, the MC3/4R agonist, MTII (10 ng/h, 0.5 μl/h, Polypeptide Laboratories), was infused intracerebroventricularly for 10 days via osmotic minipump as described above ($n = 5$). On the 10th day of MTII infusion at 10 ng/h, the rats were lightly anesthetized with isofluorane and the osmotic minipump was replaced by another pump to deliver the agonist at a higher concentration (50 ng/h).

In a separate experiment, diabetic rats ($n = 5$) were treated with MTII at the dose of 10 ng/h and were pair-fed the same amount of food consumed by diabetic rats during chronic leptin intracerebroventricular infusion.

Chronic intracerebroventricular leptin infusion during MC3/4R blockade ($n = 5$). Five days after STZ injection, the MC3/4R antagonist SHU-9119 (1 nmol/h, 0.5 μl/h; Polypeptide Laboratories) was infused intracerebroventricularly for 17 days via osmotic minipump as described above. After the first 7 days of intracerebroventricular SHU-9119 infusion, an additional minipump was implanted 1–2 cm apart from the other minipump and connected to the intracerebroventricular cannula via a Y connector to deliver leptin intracerebroventricularly for 10 days at 0.62 μg/h. The rate of SHU-9119 infusion was based on our previous study showing that this dose effectively blocks the MC3/4R and the chronic dietary and cardiovascular effects of leptin in normal Sprague-Dawley rats (9). Blood glucose concentration was measured each morning between 9:00 and 10:00 A.M. for determination of blood glucose levels using glucose strips (Reli On).

Statistical analysis. The data are expressed as mean ± SE and analyzed by using two-factor ANOVA with repeated measures. The Bonferroni post hoc test was used for comparisons between groups. Dunnett's test was used for comparisons of experimental and control values within each group, when appropriate. Statistical significance was accepted at a level of $P < 0.05$.

RESULTS

Effects of induction of diabetes and chronic intracerebroventricular leptin infusion on appetite, blood glucose, and cardiovascular function. Induction of insulin-deficient diabetes with STZ was associated with rapid development of hyperglycemia (433 ± 28 mg/100 ml on day 5 post-STZ injection, Fig. 1*B*, Table 1), hyperphagia (from 22 ± 1 g/day in the control period to 45 ± 2 g/day on day 5 after STZ injection, Fig. 1*A*), and increased water intake and urine volume (Table 1).

Induction of STZ-diabetes also caused marked bradycardia with heart rate rapidly falling by as much as −77 bpm 5 days after STZ injection (Fig. 2*A*). MAP responses after the induction of diabetes were variable among the groups but remained unchanged on average during the first 5 days after induction of diabetes (Fig. 2*B*). We previously showed that it takes ~10–15 days after the STZ injection for a significant reduction in MAP (11).

Chronic intracerebroventricular leptin infusion for 10 days in diabetic rats decreased food intake from 45 ± 2 g/day to an average of 16 ± 1 g/day during the last 5 days of leptin infusion (Fig. 1*A*) and reduced blood glucose levels all the way back to pre-diabetic control values (118 ± 19 mg/100 ml, Fig. 1*B*, Table 1).

The normalization of blood glucose levels by intracerebroventricular leptin infusion was accompanied by a marked reduction in urine volume and water intake to values similar to pre-diabetic levels (Table 1). In addition, chronic leptin treatment reversed the bradycardia and raised heart rate by ~40–50 bpm above the pre-diabetic control values (Fig. 2*A*). Although leptin tended to raise MAP, the increase was not significant compared with the day before leptin infusion was started (Fig. 2*B*).

Effects of chronic intracerebroventricular infusion of MC3/4R agonist on appetite, blood glucose, and cardiovascular function. Chronic intracerebroventricular infusion of the MC3/4R agonist, MTII, at a dose of 10 ng/h for 10 days in ad libitum–fed diabetic rats caused only a transient reduction in food intake lasting for ~3–4 days, after which food intake returned to values observed before the MTII infusion was started (Fig. 1*B*). During the course of the 10-day treatment period, food intake continued to rise to a level that was more than double the initial control level. A similar pattern was observed for the effects of MTII on blood glucose levels, except for the less pronounced initial reduction in glucose levels (Fig. 1*A*). Chronic MC3/4R activation also resulted in a transient reduction in water intake and urine output, in parallel with the transient changes in blood glucose levels (Table 1).

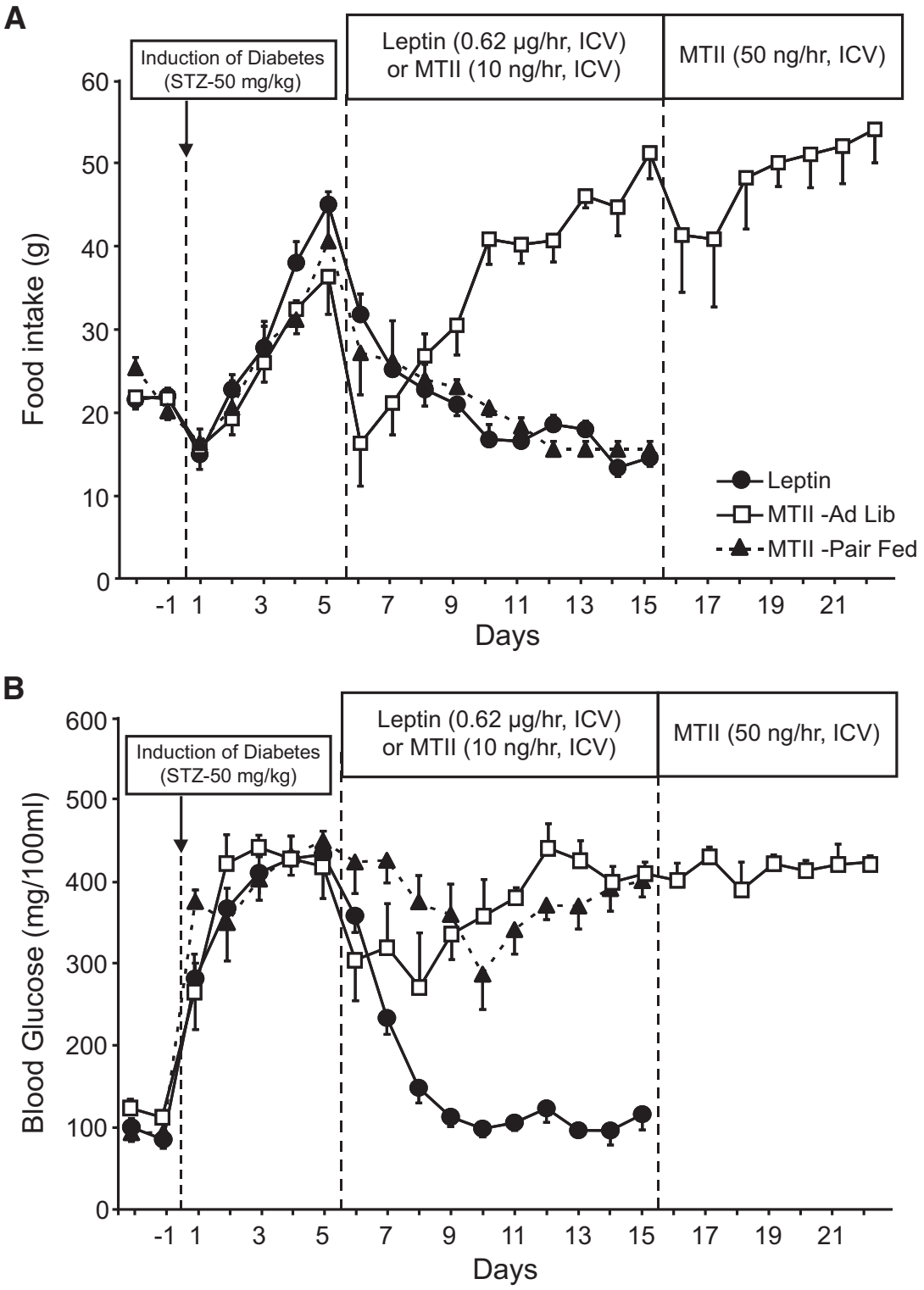

FIG. 1. Food intake (*A*) and blood glucose (*B*) responses to chronic intracerebroventricular infusion of leptin (●, $n = 5$) or the MC3/4R agonist MTII in ad libitum–fed (□, $n = 5$) and pair-fed (▲, $n = 5$) STZ-diabetic rats. Data are means ± SE.

Chronic MC3/4R activation in ad libitum–fed diabetic rats also attenuated the bradycardia associated with induction of diabetes and raised heart rate by ~50 bpm during the initial 5 days of infusion (Fig. 2*A*). However, this effect waned on days 6–7 of MTII infusion and heart rate gradually fell. We also observed a 10-mmHg initial elevation in MAP during the first 5–6 days of MTII infusion that was followed by a return of MAP to the same values observed on the day before MTII treatment was initiated (Fig. 2*B*).

A fivefold increase in the dose of MTII from 10–50 ng/h had no additional effect to prevent the hyperphagia, hyperglycemia, and bradycardia associated with STZ-induced diabetes (Fig. 1*A* and *B*). These results indicate that chronic MC3/4R activation alone does not recapitulate the long-term effects of leptin on food intake, glucose ho-

TABLE 1
Blood glucose, water intake, and urine output in STZ-diabetic rats treated with leptin alone (0.62 μg/h i.c.v.) or during MC3/4R antagonism with SHU-9119 (1 nmol/h i.c.v.) and in diabetic rats fed ad libitum or pair-fed that were infused with the MC3/4R agonist MTII (10 ng/h i.c.v.)

	Glucose (mg/100 ml)	Water intake (ml/day)	Urine output (ml/day)
Leptin group			
Control	99 ± 5	8 ± 2	45 ± 2
STZ—day 5	433 ± 28*	211 ± 20*	161 ± 21*
Leptin—day 10	118 ± 19	6 ± 3	54 ± 4
MTII ad libitum group			
Control	112 ± 3	11 ± 2	39 ± 4
STZ—day 5	418 ± 43*	139 ± 16*	198 ± 18*
MTII (10 ng/h)—day 2	319 ± 53*†	42 ± 15*†	83 ± 22*†
MTII (10 ng/h)—day 10	401 ± 18*	245 ± 34*†	300 ± 43*†
MTII (50 ng/h)—day 2	429 ± 12*	159 ± 23*	213 ± 30*
MTII (50 ng/h)—day 7	423 ± 13*	303 ± 20*†	358 ± 19*†
MTII pair-fed group			
Control	97 ± 6	12 ± 2	45 ± 3
STZ—day 5	449 ± 20*	193 ± 23*	241 ± 18*
MTII (10 ng/h)—day 2	426 ± 27*	141 ± 32*	177 ± 30*
MTII (10 ng/h)—day 10	401 ± 19*	71 ± 21*†	103 ± 24*†
Leptin + SHU-9119 group			
Control	114 ± 4	9 ± 1	41 ± 3
STZ—day 5	442 ± 42*	144 ± 15*	189 ± 18*
SHU-9119—day 7	440 ± 21*	268 ± 17*†	326 ± 19*†
Leptin + SHU-9119—day 10	436 ± 14*	350 ± 34*†	419 ± 37*†

Values expressed are for day 5 of control period, 5 days after injection of STZ, and during the experimental periods as indicated in the table. Note: Total daily fluid intake equals the water plus a fixed continuous intravenous saline infusion (40 ml/day, 0.45% saline) throughout the study. *$P < 0.05$ compared with control; †$P < 0.05$ compared with STZ—day 5.

meostasis, and cardiovascular function in this model of diabetes.

Inclusion of a group of pair-fed diabetic rats treated with MTII to match the amount of food consumed by the leptin-treated group showed no additional effects of the pair-feeding on the long-term actions of MC3/4R activation on appetite, glucose homeostasis, or cardiovascular function in STZ-diabetic rats (Fig. 1*A* and *B*, Table 1). These results suggest that changes in food intake cannot explain the lack of sustained long-term metabolic and cardiovascular actions during MC3/4R activation.

Effects of chronic intracerebroventricular leptin infusion on appetite, glucose levels, and cardiovascular function during MC3/4R antagonism. Although chronic MTII intracerebroventricular infusion for 17 days did not mimic the results observed in the leptin-treated group, a functional MC3/4R is required for leptin to exert its metabolic and cardiovascular effects in diabetic rats. Chronic blockade of MC3/4R, using SHU-9119, completely abolished the effects of leptin to reduce food intake and to restore euglycemia in STZ-diabetic rats. Food intake remained elevated at 57 ± 2 g/day and blood glucose averaged 436 ± 14 mg/100 ml on day 10 of leptin plus SHU-9119 intracerebroventricular infusion (Fig. 3*A* and *B*). The inability of leptin to reduce blood glucose levels and food consumption during MC3/4R antagonism was also reflected in the maintenance of markedly elevated water intake and urine output during intracerebroventricular leptin infusion, in contrast to the effects of leptin to completely restore these variables to pre-diabetic levels in rats with intact MC3/4R function (Table 1).

In addition to preventing the antidiabetic and anorexic actions of leptin, SHU-9119 treatment also abolished the rise in heart rate during intracerebroventricular leptin infusion; heart rate continued to fall during leptin treatment (−137 ± 11 bpm on the last day of intracerebroventricular leptin infusion, Fig. 4*A*). MC3/4R antagonism also blocked leptin's ability to prevent the fall in MAP normally observed when STZ-induced diabetes is maintained for periods longer than 2 weeks (92 ± 3 vs. 80 ± 3 mmHg for control and the last day of intracerebroventricular leptin infusion, respectively; Fig. 4*B*).

DISCUSSION

There are two major findings of this study. First, we demonstrated that the chronic antidiabetic, appetite, and cardiovascular actions of leptin in insulin-deficient STZ-diabetic rats require a functional CNS melanocortin system and ultimately activation of MC3/4R; blockade of these receptors completely prevented the chronic effects of leptin on food and water intake, blood glucose, heart rate, blood pressure, and urine volume. Second, chronic MC3/4R activation alone transiently reduced appetite and blood glucose while raising heart rate in diabetic rats, but these effects gradually waned and did not mimic the responses observed during chronic hyperleptinemia. These results indicate that activation of the MC3/4R is required for leptin to exert its metabolic and cardiovascular actions, but is apparently not sufficient to mimic these actions of leptin that may involve interactions of multiple pathways.

It is likely that other systems are triggered during prolonged MC3/4R stimulation to offset the reductions in food intake and blood glucose as well as the MAP and heart rate responses to MC3/4R activation. The identity of these compensatory systems is still uncertain, but may involve activation of orexigenic factors known to be suppressed by leptin (i.e., NPY, melanin-concentrating hormone, AGRP, and others) and/or downregulation of anorexigenic factors that are stimulated by leptin (i.e., corticotrophin-releasing hormone, cocaine-amphetamine–related peptide, and brain-derived neurotrophic factor, for example). It is possible that leptin-induced changes in one or more of these factors also contribute to the powerful antidiabetic effect of leptin and additional studies will be needed to answer these questions.

The observation that MC3/4R antagonism abolished the antidiabetic and cardiovascular actions of leptin is consistent with our previous finding that an intact hypothalamic MC3/4R is necessary for leptin to reduce food intake and fasting insulin levels and to raise heart rate and blood pressure in normal nondiabetic rats (9). However, the long-term responses to MC3/4R activation by MTII infusion in STZ-diabetic rats differed from our previous observations in nondiabetic rats where, despite not causing sustained reductions in food intake, the elevations in heart rate and MAP were maintained through the entire period of MTII treatment (22,23). Increasing the dose of MTII fivefold did not alter the responses when compared with the lower dosage, indicating that the waning responses are not likely to be caused by an insufficient level of MC3/4R activation in diabetic rats. One possible explanation for these differences is that activation of compensatory mechanisms during chronic MC3/4R activation is even more

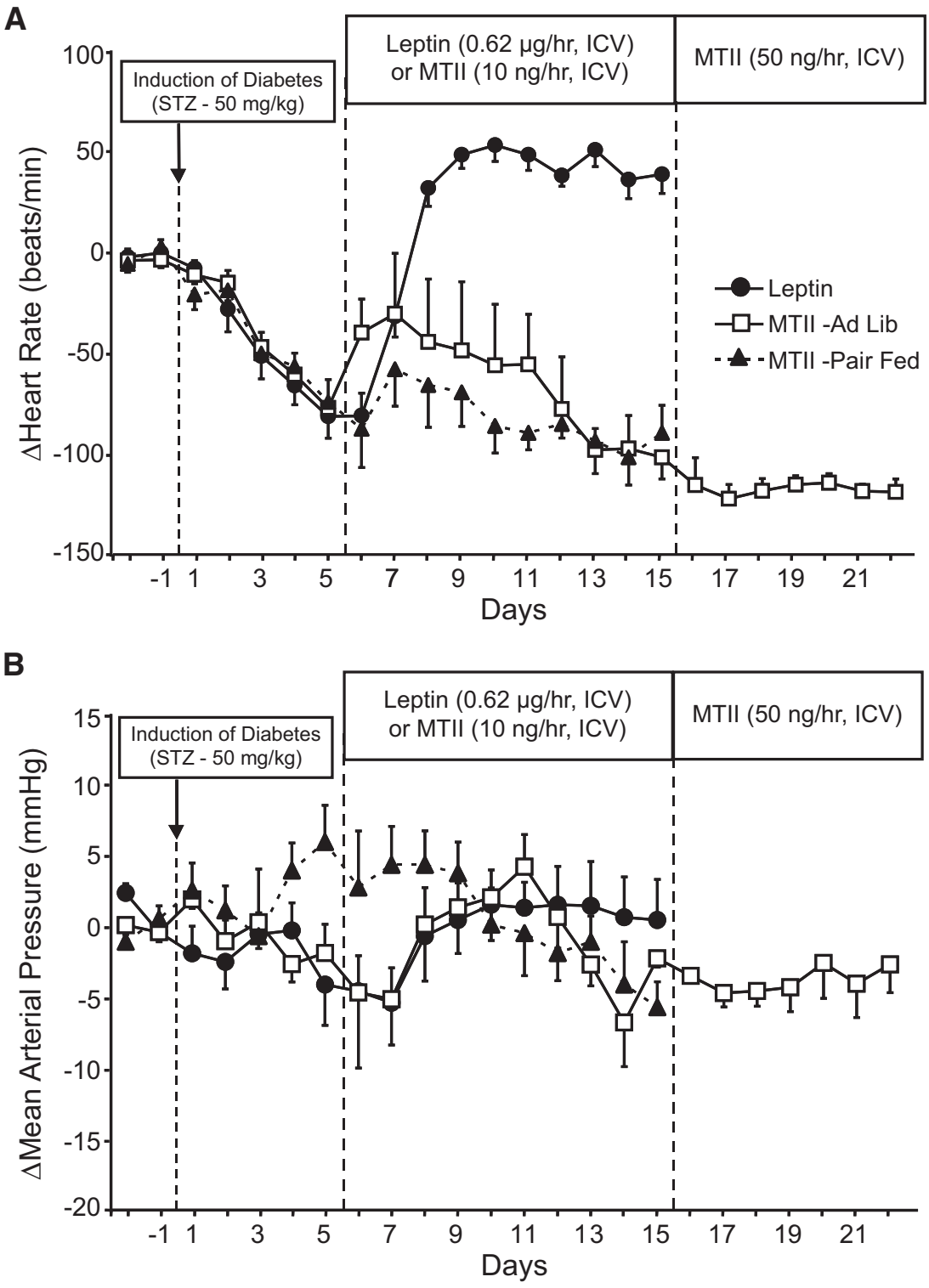

FIG. 2. Heart rate (*A*) and MAP (*B*) responses to chronic intracerebroventricular infusion of leptin (●, *n* = 5) or the MC3/4R agonist MTII in ad libitum–fed (□, *n* = 5) and pair-fed (▲, *n* = 5) STZ-diabetic rats. Baseline heart rate and MAP values for leptin, MTII ad libitum–fed, and MTII pair-fed groups were 378 ± 5 bpm and 100 ± 3 mmHg, 366 ± 11 bpm and 90 ± 1 mmHg, and 398 ± 8 bpm and 101 ± 4 mmHg, respectively. Data are means ± SE.

pronounced in diabetes than under normal conditions. For instance, in STZ-induced diabetes, NPY/AGRP neurons are markedly activated and may play a major role in promoting the hyperphagia in this model of diabetes (24,25).

Another possible explanation for the inability of chronic MC3/4R activation to mimic the antidiabetic effects of leptin is that MC3/4R may have only a short-term anorectic action and that the initial fall in blood glucose is mainly caused by a reduction in food intake. It could be hypothesized that the hyperphagia in diabetes and increased intake of glucose and other nutrients (fat and proteins) that can be transformed into glucose overcomes the effects of MC3/4R to lower blood glucose. To test this hypothesis, we studied a group of diabetic rats in which

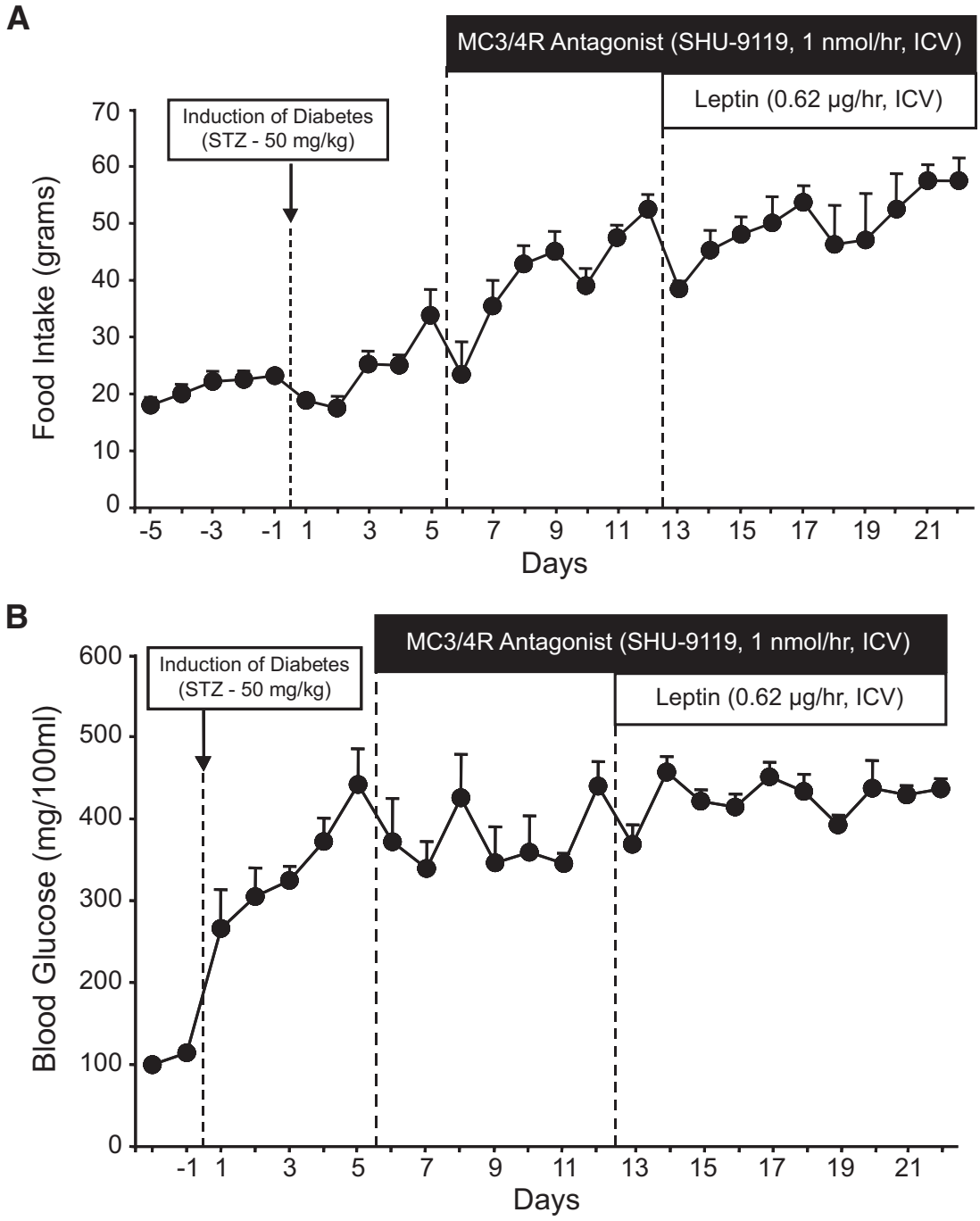

FIG. 3. Food intake (*A*) and blood glucose (*B*) responses to chronic intracerebroventricular infusion of MC3/4R antagonist (SHU-9119) and leptin during SHU-9119 infusion in STZ-diabetic rats ($n = 5$). Data are means ± SE.

food intake was prevented from increasing by pair-feeding them to match the amount of food consumed by the leptin-treated group. Preventing the hyperphagia, however, did not improve the effectiveness of MTII to lower blood glucose levels, suggesting that the lack of sustained antidiabetic effect during chronic MC3/4R activation was not because of MTII inability to reduce appetite. These results also confirm our previous observation that the reduction of food intake in diabetic rats during intracerebroventricular leptin infusion does not play a major role in mediating the antidiabetic actions of leptin or in preventing the cardiovascular alterations associated with uncontrolled diabetes (11).

The precise mechanisms by which leptin exerts its powerful effect on peripheral glucose utilization even in insulin-deficient diabetic animals are still unclear, although our current study clearly indicates that a functional MC3/4R plays a crucial role. Previous studies have implicated a role for the autonomic nervous system in mediating the acute effects of leptin on glucose regulation by showing that the increased insulin sensitivity observed during intracerebroventricular injection of single doses of leptin can be blocked by adrenergic receptor antagonism (26,27), or that leptin's ability to suppress liver glucose production can be prevented by denervation of the vagal fibers innervating the liver (28). We recently showed that

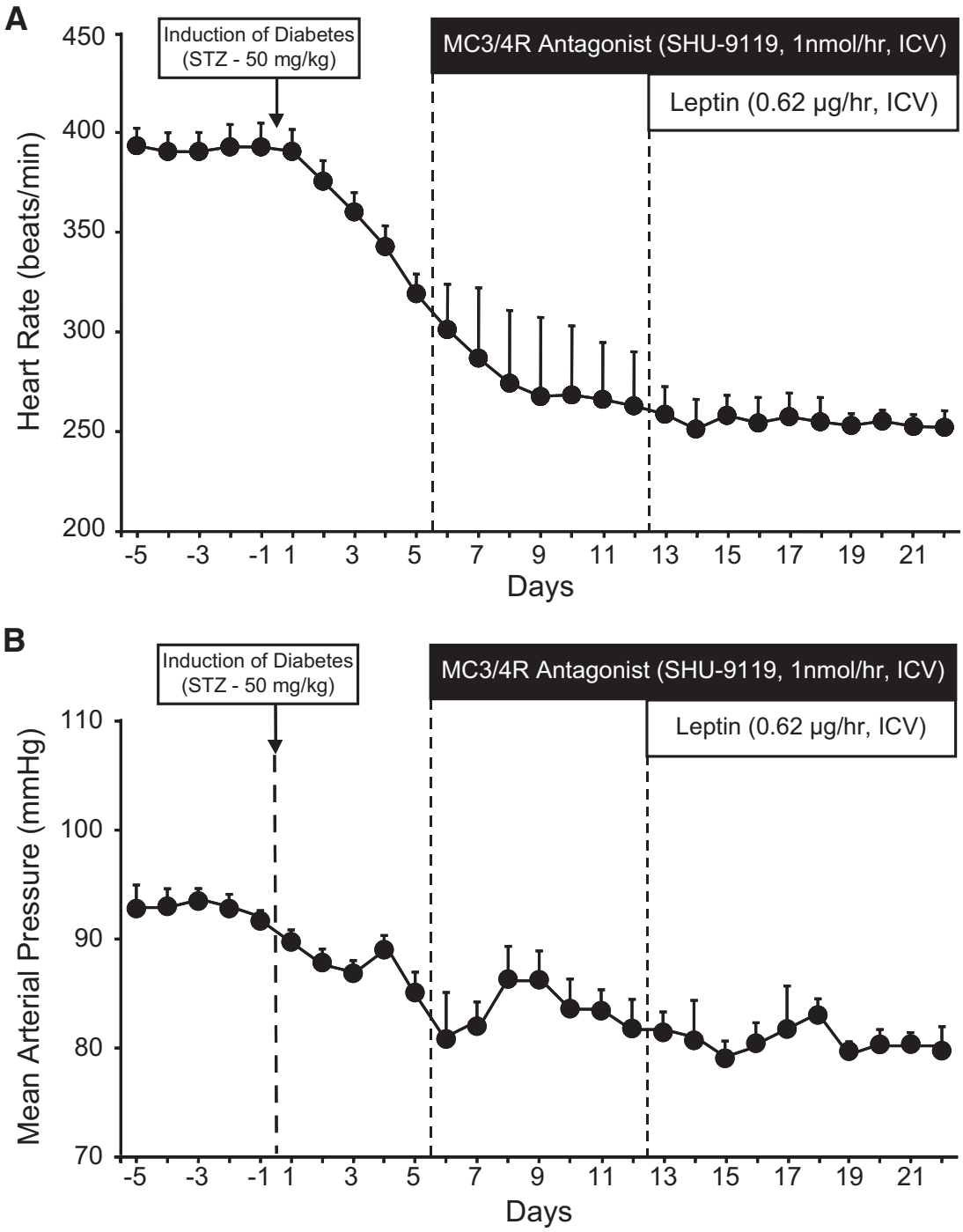

FIG. 4. Heart rate (*A*) and MAP (*B*) responses to chronic intracerebroventricular infusion of MC3/4R antagonist (SHU-9119) and leptin during SHU-9119 infusion in STZ-diabetic rats ($n = 5$). Data are means ± SE.

chronic blockade of the α1, β1, β2, and β3 adrenergic receptors failed to attenuate leptin's ability to restore euglycemia in STZ-diabetic rats (11). Therefore, it is possible that leptin-induced sympathetic stimulation of nonadrenergic receptors may contribute to these effects of leptin and that the suppression of liver glucose output into the systemic circulation of diabetic rats may play an important role in mediating the chronic effects of leptin on glucose homeostasis, but additional studies are needed to test these possibilities.

Although our previous study indicates that adrenergic receptor activation does not mediate the chronic antidiabetic effects of leptin, ~40–50% of the rise in heart rate and prevention of the bradycardia in STZ-diabetic rats during leptin infusion was dependent of adrenergic stimulation (11). The mechanisms responsible for the remaining 50–60% of leptin-induced rise in heart rate in diabetic rats are not well understood. However, the bradycardia caused by induction of STZ-diabetes is associated with marked reductions in the intrinsic heart rate (29), which is the heart rate in the absence of sympathetic and parasympathetic inputs to the heart. Moreover, chronic intracerebroventricular leptin infusion completely restored intrinsic heart rate back to pre-diabetic values (29). We

have also shown that, similar to leptin, MC3/4R activation is associated with sustained sympathetic nervous system activation in nondiabetic rats (30). Whether the lack of sustained increases in heart rate during MTII in STZ-diabetic is because of an inability of chronic MC3/4R activation to cause sustained elevations in cardiac sympathetic activity in a hyperglycemic state or to an inability to increase intrinsic heart rate remains to be determined.

In summary, leptin has powerful CNS-mediated antidiabetic effects in insulin-deficient diabetic rats that require activation of the CNS melanocortin pathway. Leptin also exerts important cardiovascular effects that require activation of CNS MC3/4R. However, stimulation of the CNS MC3/4R alone does not confer the same long-term metabolic and cardiovascular responses as observed with hyperleptinemia. These observations indicate that although leptin-mediated activation of the melanocortin pathway may be necessary for the antidiabetic and cardiovascular actions of leptin in this model, it is not sufficient to completely mimic leptin's chronic actions. This suggests that leptin exerts its CNS-mediated effects on appetite, blood glucose, MAP, and heart rate via a complex system that likely involves interaction of multiple pathways. Unraveling these interactions would contribute to a better understanding of the CNS control of appetite, glucose homeostasis, and cardiovascular function and could lead to the development of novel therapeutic strategies to treated obesity, metabolic syndrome, diabetes, and cardiovascular diseases.

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