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Sympathoadrenal Responses to Glucoprivation and Lipoprivation in Rats

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SCHEURINK, A. AND S. RITTER. *Sympathoadrenal responses to glucoprivation and lipoprivation in rats.* *PHYSIOL BEHAV* 53(5) 995-1000, 1993.—The effects of glucoprivation and lipoprivation on sympathoadrenal outflow were investigated in rats with permanent intra-atrial catheters. Glucoprivation was induced by infusion of a hypoglycemic dose of insulin (3 U/kg) or by infusion of the glucose antimetabolite, 2-deoxy-D-glucose (2-DG, 200 mg/kg). Lipoprivation was induced by infusion of sodium mercaptoacetate (MA, 600 μ mol/kg), which blocks beta oxidation of fatty acids. Stress-free blood samples for measurement of blood glucose, plasma nonesterified fatty acids (NEFA), and epinephrine (E) and norepinephrine (NE) concentrations were collected remotely before and after drug injection. Glucoprivation and lipoprivation differed significantly in their effects on the sympathoadrenal system. Both 2-DG- and insulin-induced glucoprivation appeared to increase adrenomedullary secretion selectively, leading to dramatically increased plasma E levels. Although plasma NE levels also rose during glucoprivation, other evidence suggests that this effect may be secondary to the rise in E. In contrast, MA-induced lipoprivation increased the outflow of NE from the sympathetic nerve endings without a significant effect on plasma E concentrations. Plasma E levels rose only late in the test, as blood glucose levels began to fall. Results indicate that glucoprivation and lipoprivation are distinct metabolic signals, each capable of selectively activating one branch of the sympathoadrenomedullary system and thereby facilitating the mobilization of metabolic fuels appropriate for the specific metabolic challenge.

Insulin-induced hypoglycemia 2-DG Mercaptoacetate Glucose Epinephrine Norepinephrine

INITIATION of food intake and activation of the sympathoadrenal system appear to be the primary behavioral and neuroendocrine responses to a reduction in the availability of energy substrates (3,29). These behavioral and sympathoadrenal responses act in a coordinated fashion to mobilize, redistribute, and replenish metabolic fuels.

With respect to food intake, two specific metabolic controls, the glucoprivic and the lipoprivic controls, have been identified (2,11,15,21). These controls stimulate feeding in response to decreased glucose utilization (glucoprivation) or decreased fatty acid oxidation (lipoprivation) and can be experimentally activated by administration of hypoglycemic doses of insulin (11,21,25), by glucose antimetabolites such as 2-deoxy-D-glucose (2-DG) (1,11,21), or by drugs that block fatty acid oxidation, such as sodium mercaptoacetate (MA) (2,12,13,15).

With respect to the effects of specific metabolic deficits on sympathoadrenal activation, only glucoprivation has been studied. Both insulin-induced hypoglycemia (3) and 2-DG-induced blockade of intracellular glucose metabolism (9) stimulate sympathoadrenal activity, thereby elevating plasma levels of the catecholamines epinephrine (E) and norepinephrine (NE). However, the effects of lipoprivation on sympathoadrenal activity

have not yet been examined. Therefore, the primary goal of this experiment was to examine and compare the effects of systemic 2-DG- and insulin-induced glucoprivation with MA-induced lipoprivation on sympathoadrenal activity and circulating metabolic fuels.

Most previous studies on the effects of glucoprivation on sympathoadrenal outflow have been performed in anesthetized animals. Anesthesia itself, however, markedly alters sympathetic outflow and inhibits adrenal catecholamine release during stress (3,26). Therefore, an important aspect of the present study is that the sympathoadrenal catecholamine responses to glucoprivation and lipoprivation were measured by remote blood sampling in conscious, freely behaving rats that were permanently cannulated and well habituated to the experimental procedures prior to testing. Such procedures have been shown to be sensitive and appropriate for accurate assessment of both basal and stimulated levels of sympathoadrenal outflow (18,19,23).

Results of this study indicate that glucoprivation and lipoprivation are distinct metabolic signals, each capable of selectively activating one branch of the sympathoadrenomedullary system (the adrenomedullary or sympathetic neuronal branch, respectively). These selective responses result in the mobilization

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of metabolic fuels appropriate for each specific metabolic challenge.

METHOD

Animals and Housing

Male Sprague-Dawley rats obtained from the Washington State University Laboratory Animal Resource Center, weighing 260–320 g at the beginning of the present experiments, were used. The animals were individually housed in Plexiglas cages at room temperature ($20 \pm 2^\circ\text{C}$), and had continuous access to medium fat, high-carbohydrate food (12,15) and water unless otherwise stated. The rats were maintained on a 12–12 h light–dark regime (0700–1900 h light), and they were handled and weighed every day at 0900 h.

Heart Cannulation

Surgery was performed under methoxyflurane (Metaflane, Pitman Moore) anesthesia. All animals were provided with a silicon heart catheter (0.95 mm o.d., 0.50 mm i.d.), inserted into the heart through the left jugular vein and externalized on the top of the skull according to techniques described earlier (24). This method allows intravenous infusion and frequent repeated blood sampling in unanesthetized, undisturbed, freely moving animals (23). The rats were habituated to the blood-sampling procedures prior to the start of the experiments. The experiments were initiated 1 week after surgery when the rats were above their preoperative weights.

Blood Sampling and Chemical Determinations

All experiments were performed in the light period between 0900 and 1200 h after overnight food deprivation. Forty minutes before the first blood sample was taken, the animals were connected to a polyethylene blood-sampling tubing (in mm: 300 length, 1.25 o.d., 0.75 i.d.). For each experiment, 11 blood samples of 0.3 ml each were taken from each rat for determination of blood glucose and catecholamine levels (Experiments 1–3) and plasma free fatty acids (Experiment 3). After each blood sample, a transfusion of the same amount of donor blood was given to avoid diminution of the blood volume with related changes in hemodynamics. Donor blood was obtained from undisturbed donor rats with permanent heart catheters. Heparin was used as the anticoagulant for Experiments 1 and 2. Since heparin is known to stimulate lipoprotein lipase and thereby release free fatty acids, citrate rather than heparin was used as the anticoagulant in Experiment 3.

Blood samples were immediately transferred to chilled (0°C) centrifuge tubes containing 0.1% EDTA as antioxidant and 10 μl heparin solution (500 U/ml) as anticoagulant. Blood glucose was measured by the glucose oxidase method (14) with 0.05 ml blood taken from the sample. The remaining part was centrifuged for 15 min at 5000 rpm at 4°C , and the supernatant was immediately stored at -80°C . Plasma catecholamine concentrations were determined by high pressure liquid chromatography (HPLC) in combination with electrochemical detection (ECD). The protocol for catecholamine determination was slightly modified from published procedures (10). The HPLC-ECD system included an LKB 2150 pump (LKB Instruments, Bromma, Sweden), a Rheodyne injection valve with a 100 μl loop, a reversed-phase nucleosil C18 column (length 25 cm, i.d. 4 mm) (Gimex, The Netherlands) held at 30°C by a column stove (LKB), an ESA 5100 A electrochemical detector with a 5011 high-sensitive analytical cell and a 5020 guard cell (ESA), and a BD 41 two-channel flat recorder (Kipp). Guard cell potential

in front of the injection valve was +450 mV; the potentials of the working electrodes were -50 mV and $+350$ mV, respectively. The mobile phase contained 0.05 M Na-acetate, 0.08% heptane sulfonic acid, 0.01% EDTA, 0.01% NaCl, and 5% methanol 95% H_2O (pH 4.75). The limit of the detection level for epinephrine was 0.010 ng/ml and 0.005 ng/ml for norepinephrine. Intra- and interassay coefficients of variation for the catecholamine measurements were 2.25% and 5.36%, respectively. Determination of plasma nonesterified fatty acids (NEFA) was performed in triplicate 20- μl plasma samples assayed with a WAKO NEFA kit.

Experiments

The aim of the present study was to investigate the effects of glucoprivation and lipoprivation on the outflow of catecholamines from the adrenal medulla and the nerve endings of the sympathetic nervous system. Therefore, rats were subjected to insulin-induced hypoglycemia, intravenous administration of 2-deoxy-D-glucose, and blockade of fatty acid oxidation with sodium mercaptoacetate. These experiments were designated Experiments 1 to 3, respectively. In all experiments, two blood samples were taken before administration of the drug to measure baseline levels of the blood components. The experimental drug was intravenously injected at $t = 0$ min. Blood samples were taken before and after injection at the time points $t = -11, -1, 2.5, 5, 7.5, 10, 15, 30, 45, 60,$ and 75 min relative to the administration of the drug.

In Experiment 1, the effects of intravenous administration of a single dose of insulin (NOVO Nordisk Pharmaceuticals Inc, 3 U/kg) on sympathoadrenal outflow were investigated in six rats. Blood glucose concentrations were measured in all blood samples, and plasma norepinephrine and epinephrine levels were determined in the samples taken at the time points $t = -11, -1, 2.5, 5, 7.5, 10, 45,$ and 75 min.

In Experiment 2, the effects of intravenous administration of a single dose of 2-DG (Sigma, 200 mg/kg) on sympathoadrenal outflow were investigated in six rats. Blood glucose concentrations were measured in all blood samples, and plasma E and NE levels were determined in the samples taken at the time points $t = -11, -1, 5, 10, 45,$ and 75 min.

Finally, in Experiment 3, the effects of intravenous administration of a single dose of MA (thioglycolic acid, Sigma, 600 $\mu\text{mol/kg}$) on sympathoadrenal outflow were investigated in six rats. Blood glucose, plasma NEFA, and plasma E and NE concentrations were measured in all blood samples.

Data Analysis and Statistics

Data are expressed as averages \pm SE. Wilcoxon matched-pairs signed rank test was used to compare the levels of the blood components relative to the baseline level at $t = -1$ min. Significance was set at $p < 0.05$.

RESULTS

Experiment 1: Insulin-Induced Hypoglycemia

The results from Experiment 1 are presented in Fig. 1. Injection of insulin immediately decreased blood glucose concentrations from baseline levels of 75 ± 7 mg/dl at $t = -1$ min to a minimum of 29 ± 2 mg/dl at $t = 60$ min. The decrease of blood glucose was significant at all time points after injection of insulin. Plasma E levels increased during insulin-induced hypoglycemia from baseline concentrations of 0.09 ± 0.03 ng/ml at $t = -1$ min up to a maximum of 4.73 ± 0.98 ng/ml at $t = 60$ min. The increase of plasma E was significant at all time

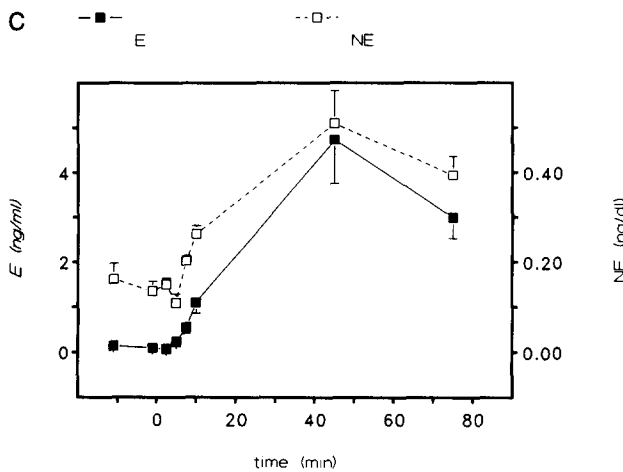
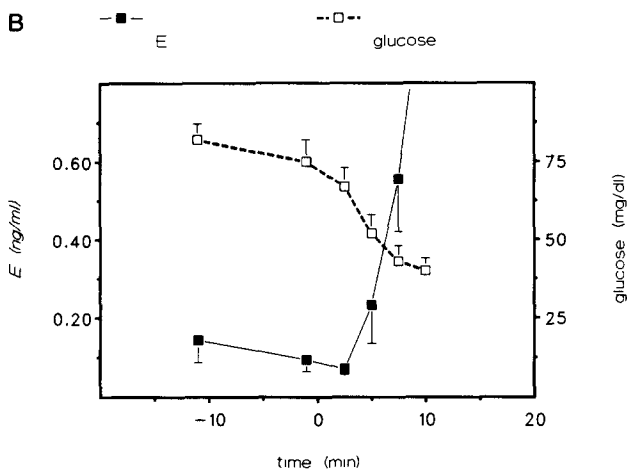
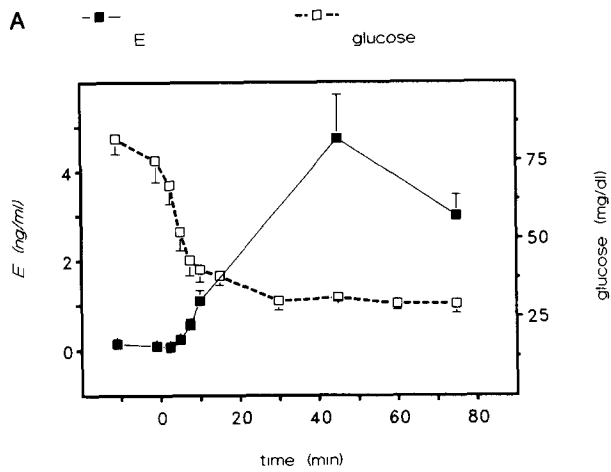


FIG. 1. (A) Blood glucose and plasma epinephrine (E) concentrations in mg/dl and ng/ml, respectively, before and after a single intravenous injection of insulin (3 U/kg). Data are expressed as averages \pm SE. (B) Blood glucose and plasma E concentrations in mg/dl and ng/ml, respectively, before and immediately after a single intravenous injection of insulin (3 U/kg). Data are expressed as averages \pm SE. (C) Plasma E and norepinephrine (NE) concentrations in ng/ml before and after a single intravenous injection of insulin (3 U/kg). Data are expressed as averages \pm SE.

points after $t = 5$ min. Epinephrine levels started to increase when blood glucose levels were between 67 and 52 mg/dl (Fig. 1C). Plasma NE levels moderately increased from baseline levels of 0.14 ± 0.2 at $t = -1$ min up to 0.50 ± 0.07 at $t = 45$ min during insulin-induced hypoglycemia. The increase of NE was significant at all time points after $t = 7.5$ min.

Experiment 2: 2-Deoxy-D-Glucose

The results from Experiment 2 are presented in Fig. 2. Blood glucose levels immediately increased after injection of 2-DG from baseline levels of 73 ± 5 mg/dl up to a maximum of 208 ± 13 mg/dl at $t = 60$ min. Also, plasma E and NE concentrations increased after 2-DG injection (from baseline levels of 0.03 ± 0.002 and 0.118 ± 0.03 ng/ml at $t = -1$ min to maximal levels of 3.94 ± 0.82 and 0.39 ± 0.07 at $t = 45$ min, respectively). The increases of blood glucose and plasma E were significant at all time points after injection of 2-DG. Plasma NE levels were significantly increased at time point $t = 45$ min.

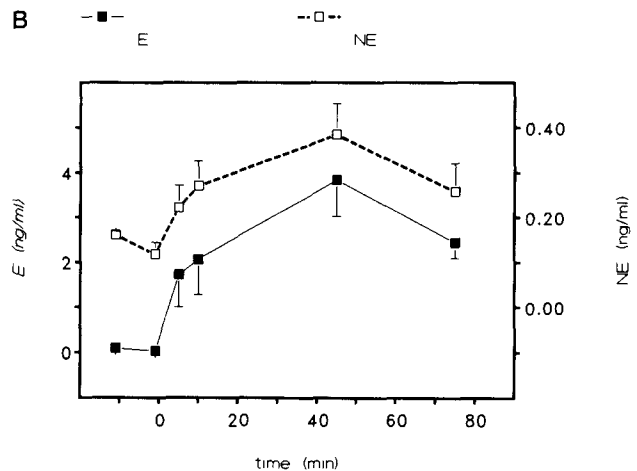
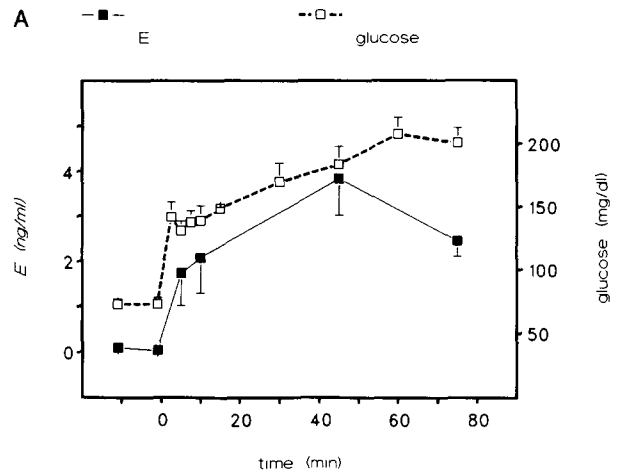


FIG. 2. (A) Blood glucose and plasma epinephrine (E) concentrations in mg/dl and ng/ml, respectively, before and after a single intravenous injection of the glucose antimetabolite 2-deoxy-D-glucose (2-DG, 200 mg/kg). Data are expressed as averages \pm SE. (B) Plasma E and norepinephrine (NE) concentrations in ng/ml before and after a single intravenous injection of the glucose antimetabolite 2-DG (200 mg/kg). Data are expressed as averages \pm SE.

Experiment 3: Mercaptoacetate

The results from Experiment 3 are presented in Fig. 3. Injection of MA caused an increase of blood glucose from baseline levels of 85 ± 5 mg/dl up to a maximum of 113 ± 5 at $t = 15$ min after injection. The increase of blood glucose was significant at the time points $t = 5, 10, 15,$ and 30 min. Blood glucose then declined to levels below baseline (significant at $t = 75$ min when blood glucose levels were 65 ± 7 mg/dl).

Plasma NEFA levels immediately decreased after injection of MA from baseline levels of 0.672 ± 0.033 mEq/l to a minimum of 0.518 ± 0.046 mEq/l at time point $t = 7.5$ min. Thereafter, plasma NEFA concentrations increased dramatically to above baseline with a maximal level of 1.368 ± 0.147 mEq/l at $t = 75$ min at the termination of the experiment. Plasma levels of NEFA were significantly decreased below baseline at time point $t = 7.5$, and were significantly increased after baseline levels at all time points after $t = 15$ min.

Plasma E concentrations did not change from baseline level (0.05 ± 0.01 ng/ml) until time point $t = 60$ min. Then, an increase of plasma E levels occurred with a maximum of 0.73 ± 0.17 ng/ml at $t = 75$ min (significant at the time points $t = 60$ and 75 min). At the time points 5 to 15 min after injection of MA, a small but significant enhancement of plasma NE levels above baseline levels (from 0.18 ± 0.2 to 0.22 ± 0.01 ng/ml) occurred. Then, a further increase of plasma NE was seen with a maximum of 0.37 ± 0.05 ng/ml in the last sample of the experiment. Plasma NE levels were significantly increased above baseline concentrations at all time points between $t = 5$ and 75 min.

DISCUSSION

The most striking result of this study was the highly selective increase in plasma NE levels in response to MA-induced blockade of fatty acid oxidation. Plasma NE concentrations began to rise within minutes after MA injection and remained elevated throughout the study. In contrast, plasma E concentrations were not significantly elevated above basal levels until 60 min after MA injection. The delayed rise in plasma E did not appear to be stimulated directly by decreased fatty acid oxidation, but instead was temporally coupled with declining plasma glucose levels during the later portion of the test period. Since sympathetic nerve endings are the primary source of plasma NE in the rat (16,19), these results indicate that lipoprivation is a remarkably selective stimulus for activation of sympathetic neurons.

Plasma catecholamine responses to glucoprivation were similar to those reported previously (9). Both 2-DG and the hypoglycemic dose of insulin increased adrenomedullary secretion, as demonstrated by the marked increase of plasma epinephrine (E) concentrations. The relatively high dose of insulin used in Experiment 1 caused a very severe hypoglycemia during the last phase of the experiment. As a consequence, plasma E reached extremely high concentrations, up to 5 ng/ml. Plasma NE was also increased during glucoprivation. Previous results have demonstrated that high circulating levels of E increase plasma NE concentrations via β_2 -adrenoceptor-mediated stimulation of neuronal NE outflow (16,19). Therefore, it is likely that the increase in NE concentration during glucoprivation observed in the present study was secondary to the very large increase in plasma E. This possibility is consistent with other evidence demonstrating that glucoprivation stimulates the adrenomedullary branch but not the neuronal branch of the sympathoadrenal system (4,6,27,28). Thus, in terms of their direct effects, glucoprivation and lipoprivation may selectively activate different components of the sympathoadrenal system.

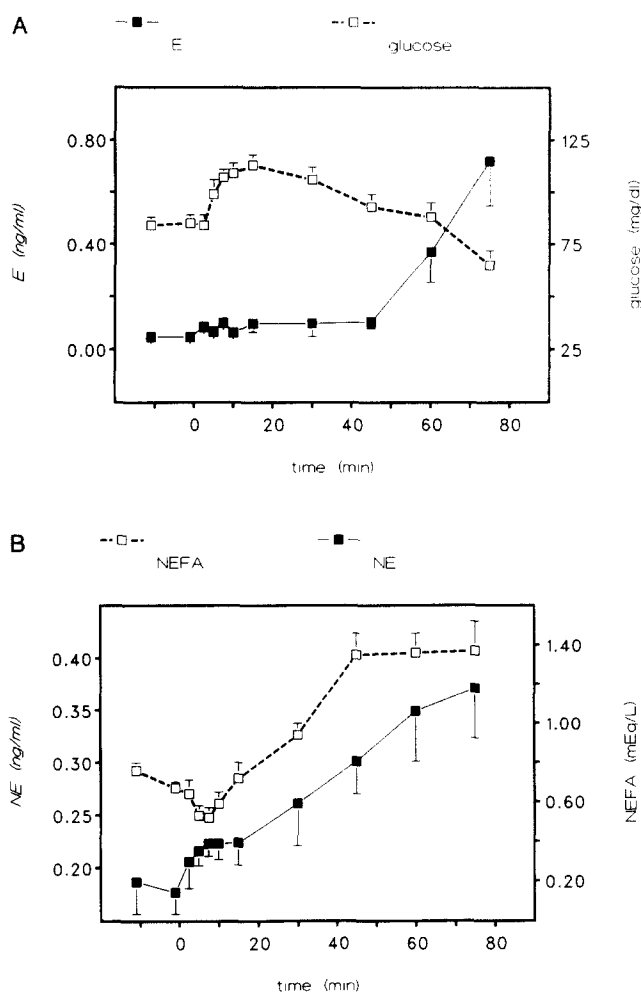


FIG. 3. (A) Blood glucose and plasma epinephrine (E) concentrations in mg/dl and ng/ml, respectively, before and after a single intravenous injection of the fatty acids antimetabolite mercaptoacetate (MA, 600 μ mol/kg). Data are expressed as averages \pm SE. (B) Plasma nonesterified fatty acids (NEFA) and norepinephrine (NE) concentrations in mEq/l and ng/ml, respectively, before and after a single intravenous injection of the fatty acid antimetabolite MA (600 μ mol/kg). Data are expressed as averages \pm SE.

As reported previously, MA increased plasma NEFA levels overall (12,15), after a small decline during the first 15 min after drug injection. The causes of the MA-induced increase in NEFA are not known. However, the present results reveal that plasma NEFA levels closely parallel the elevation in plasma NE levels. Since neuronally released NE appears to mediate white adipose tissue lipolysis (17,19), a reasonable interpretation of these results is that the MA-induced increase in plasma NEFA levels is mediated directly by the increased sympathetic neuronal release of NE, coupled with the MA-induced blockade of fatty acid utilization.

Administration of MA caused an immediate rise in blood glucose concentration. This elevation of glucose appears to be a reproducible effect of MA, since it was also observed in an earlier study in which MA was administered intraperitoneally (12). However, in contrast to results with 2-DG, the elevation in glucose by MA was not preceded by a rise in plasma E. Therefore, MA-induced elevation of blood glucose concentrations

might be mediated by a different mechanism than 2-DG-induced hyperglycemia. This mechanism may involve activation of sympathetic neuronal outflow of NE from hepatic nerve endings. Several pieces of evidence support this hypothesis. First, plasma NE levels were selectively increased by MA, indicating that sympathetic neurons were generally activated. Secondly, previous work has shown that stimulation of the sympathetic nerves to the liver may lead to an α -adrenoceptor-mediated increase of hepatic glycogenolysis (5,8,20), but that blood-borne NE does not stimulate hepatic glycogenolysis (17,19). Other mechanisms that may participate in the MA-induced increase in blood glucose, such as increased pancreatic glucagon release, decreased insulin production, or changes in adrenoceptor sensitivity to peripheral glucose metabolism, have not yet been evaluated.

After an initial increase in blood glucose levels, which peaked 15 min after MA injection, blood glucose levels began to decline slowly. Beginning 45 min after MA injection, blood glucose was reduced significantly relative to the peak values. However, blood glucose did not fall significantly below predrug baseline values until 75 min after MA injection. It is interesting to note that plasma E levels began to rise between 45 and 60 min after MA injection, when glucose levels were still above predrug baseline and above the expected threshold for stimulation of an adrenal medullary response (7). Thus, the time course of the E response suggests that sympathoadrenal activation was triggered by the relative decline of glucose levels from peak, not from baseline, values. This would suggest that a new set-point for glucose homeostasis was established during lipoprivation, determined in part by availability of NEFA as an energy substrate. Elevation of the glucose set-point by decreased metabolic availability of NEFAs might also explain why blood glucose immediately increased to a higher level after administration of MA. Future experiments are in progress to examine the influence of specific

metabolic fuels on mechanisms governing glucose homeostasis and metabolism.

In conclusion, these experiments demonstrate that glucoprivation and lipoprivation are distinct metabolic signals capable of exerting selective control of adrenomedullary and sympathetic neuronal activity, respectively. A primary function of this sympathoadrenal activation is to increase circulating levels of the deficient metabolic fuel. The evidence that decreased glucose availability exerts a powerful and selective control of adrenomedullary secretion is therefore compatible with previous findings that physiological doses of circulating E, but not NE, can stimulate hepatic glucose production in rats (17,19,22). Similarly, the selective increase in sympathetic neuronal activity induced by MA would seem to be a metabolically appropriate response to blockade of fatty acid oxidation, since previous work has demonstrated that neuronal NE, but not adrenal E, serves as the physiological mediator of lipolysis in white adipose tissue (17,19). These data indicate that mechanisms for energy homeostasis are finely tuned to detect and compensate for alterations in availability of specific metabolic fuels.

Finally, future studies are required to answer specific questions related to the subject of MA-induced outflow of neuronal NE. The present NE measurements reflect the average spillover rate of NE from many organs, which might be affected by neuronal NE release as well as NE clearance. Microdialysis will be performed to identify the vascularity in white adipose tissue as the possible source of NE. These studies can also exclude the possibility that MA might have some nonspecific effect on sympathetic activity.

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