Altered Glucose Homeostasis in Proopiomelanocortin-Null Mouse Mutants Lacking Central and Peripheral Melanocortin

UTE HOCHGESCHWENDER, JESSICA L. COSTA, PEGGY REED, STEPHANIE BUI, AND MILES B. BRENNAN

Oklahoma Medical Research Foundation (U.H., P.R., S.B.), Oklahoma City, Oklahoma 73104; and Eleanor Roosevelt Institute (J.L.C., M.B.B.), University of Denver, Denver, Colorado 80206

Prolonged obesity frequently leads to insulin resistance and, eventually, to diabetes. This relationship reflects the integration of fat stores and carbohydrate metabolism and the coordination of central nervous system functions, e.g., appetite, and peripheral metabolism. Recent work suggests that the melanocortin system is involved in this integration; specifically, central administration of melanocyte-stimulating hormone (MSH) decreases, whereas lack of central MSH signaling increases, peripheral insulin resistance. Here we asked whether MSH acting in the periphery has a complementary role in insulin resistance. We tested this in a mouse model where the proopiomelanocortin (POMC) gene encoding all of the melanocortins has been genetically deleted. The homozygous POMC-null mouse lacks central as well as peripheral MSH signaling; in addition, it lacks adrenal glands and thus is devoid of corticosterone and epinephrine. Here we report that homozygous POMC mutants have normal serum levels of insulin, normal fasting levels of glucose, and normal clearance of glucose in glucose tolerance tests. Thus, insulin production and sensitivity and glucose uptake in peripheral tissues are functioning normally. However, we found a striking inability of the homozygous POMC mutants to recover from insulin-induced hypoglycemia. This defect was in the glucagon-mediated counterregulatory response. Both peripheral administration of an MSH analog and supplementation with corticosterone alleviated the hypoglycemia after insulin challenge, but did not make the obese POMC mutant mice diabetic. We conclude that, similar to the regulation of body weight homeostasis, the regulation of glucose homeostasis requires the integration of both central and peripheral melanocortin signaling systems. (Endocrinology 144: 5194–5202, 2003)

In humans, obesity correlates to a high degree with hyperinsulinemia, insulin resistance, and hyperglycemia (1) and is the most significant risk factor for type 2 diabetes (2). Most mouse models of obesity show hyperinsulinemia and hyperglycemia to varying degrees (3). For example, the ob/ob mouse mutant lacking leptin has elevated fasting glucose levels and extreme hyperinsulinemia developing after onset of obesity, and shows decreased glucose and insulin tolerance (4, 5). The db/db mouse mutant expressing a mutant leptin receptor shows similar symptoms as the ob/ob mutant, although diabetic symptoms develop before the onset of obesity (6–8). Impairments of glucose homeostasis have also been observed in obese mouse models with genetic impairments of the melanocortin system, including melanocortin receptor 3 and 4 (MC3-R, MC4-R) knockout mutants (9), the agouti (yellow, AY, and yellow viable, AYV) mutants ectopically expressing agouti (10), and transgenic mice overexpressing the hypothalamic agouti-related protein (AGRT) (11). AGRT transgenic mice ubiquitously overexpressing AGRT, which antagonizes MC3-R and MC4-R, show hyperinsulinemia early on, followed by hyperglycemia (11). The yellow obese mouse mutant (AY/AYV) ectopically expresses the MC4-R-antagonizing agouti protein; this mutant is hyperinsulinemic and hyperglycemic (12, 13). Homozygous MC4-R-null mutants are hyperinsulinemic in males and females, whereas only males, both heterozygous and homozygous MC4-R-null mutants, are hyperglycemic by 5 months of age (14). The MC3-R mutation causes mild hyperinsulinemia in male homozygous null mutants only, with normal glucose levels (15, 16).

The proopiomelanocortin (POMC) knockout mouse (17) lacks the ligands for all melanocortin receptors, including αMSH and ACTH, and thus is deficient in melanocortin signaling at both central and peripheral sites. The homozygous POMC-null mouse mutants also lack adrenal glands and thus corticosterone and epinephrine, two other important molecules in the regulation of glucose homeostasis (18). We tested different aspects of glucose regulation in POMC-null mice to determine the effects of lack of central and peripheral melanocortin signaling and adrenal hormones on glucose homeostasis.

Materials and Methods

Animals

POMC wild-type, heterozygous, and mutant mice in the 129SvEv background (17) were housed under a 12-h light, 12-h dark cycle with a standard laboratory diet (PMI5053, Purina Mills, Richmond, IN) provided ad libitum unless otherwise stated. Mice were genotyped by PCR analysis of tail DNA (17). Mutants and wild-type, or heterozygous, littermates of strain B6.V-Lepob/lepob were obtained from The Jackson Laboratory (Bar Harbor, ME). All procedures described below follow NIH guidelines and were approved by the institutional animal care and use committee of the Oklahoma Medical Research Foundation.

Abbreviations: AGRT, Agouti-related protein; icv, intracerebroventricular; ITT, insulin tolerance test; MC3-R, melanocortin receptor 3; MSH, melanocyte-stimulating hormone; POMC, proopiomelanocortin.
Blood glucose measurements

Blood glucose levels were measured from a drop of blood from the tail vein using Bayer Glucometer Elite test strips (Bayer, Elkhart, IN).

Serum

Blood was collected into microfuge tubes from tail veins or through retroorbital phlebotomy using heparinized capillary tubes. The blood was allowed to clot at room temperature for 15 min, then was put on ice. Samples were spun at 4°C and 3500 rpm for 15 min, and serum was transferred to new microfuge tubes. Serum was flash-frozen in dry ice-ethanol and stored at −80°C until analyzed.

Glucose tolerance tests

Mice were fasted overnight and received an ip injection of glucose in normal saline (3 mg/kg body weight). Blood glucose measurements were made using tail blood as described above. Blood was sampled immediately before and at the indicated intervals after glucose injection.

Insulin tolerance tests (ITTs)

ITTs were performed on animals fasted for 5 h or overnight as indicated. Animals were injected with 1 IU/kg body weight human insulin (HumulinR, Eli Lilly & Co., Indianapolis, IN) diluted in normal saline (HumulinR, Eli Lilly & Co., Indianapolis, IN). Mice were injected with 1 IU/kg body weight human insulin (HumulinR, Eli Lilly & Co., Indianapolis, IN) diluted in normal saline or sc (ACTH) between the shoulder blades.

Corticosterone replacement

Drinking water was supplemented with corticosterone (Sigma-Aldrich Corp., St. Louis, MO) to 25 μg/ml. It was ensured that detectable levels of corticosterone were achieved by determining serum corticosterone levels from blood collected 2 h after the onset of the dark period. Corticosterone was measured using an RIA kit according to the manufacturer’s recommendations (ICN, Inc., Orangeburg, NY).

Supplementation of MSH and ACTH

The MSH analog [Ac-Cys4,7-Phe7,Cys8]αMSH-(4–13) (19) was purchased from Peninsula Laboratories (Belmont, CA). ACTH-(1–24) was synthesized by Research Genetics (Huntsville, AL). Mice were injected with peptides (1 μg, 0.1 ml PBS, and 0.5% BSA per mouse) ip (MSH analog) or sc (ACTH) between the shoulder blades.

Statistical analysis

Data were analyzed by one-way ANOVA. Significance was accepted at P < 0.05 unless indicated otherwise. Results are expressed as the mean ± SEM.

**Fig. 1.** Blood glucose and serum insulin levels in fed and fasted POMC wild-type, heterozygous, and homozygous null mice. A: ■, Wild-type; ●, heterozygous; △, mutant; ■, △, and ●, fed; □, Δ, and ○, fasted. Values represent the mean ± SEM for 4–7 males and 6–10 females/group. Note that for fed glucose levels, data points for wild-type mice and heterozygotes completely overlay. Values are not significantly different, except for fed glucose levels, [wild-type vs. homozygous mutant, males, 118 ± 2.8 vs. 166 ± 13.7 mg/dl at 3 months (P < 0.05) and 115 ± 5 vs. 156.5 ± 7.8 mg/dl at 5 months (P < 0.005); females, 99.3 ± 3.2 vs. 126.8 ± 7.9 mg/dl at 3 months (P < 0.005) and 103.3 ± 2.7 vs. 133.3 ± 3.8 mg/dl at 5 months (P < 0.0001)]. B, Body weights [wild-type vs. homozygous mutant, males, 20.9 ± 0.2 vs. 20.1 ± 1.6 g at 1 month (P = NS), 28.7 ± 0.7 vs. 41.5 ± 1.9 g at 3 months (P < 0.0005), and 28.2 ± 1.2 vs. 44.4 ± 3.9 g at 5 months (P < 0.005); females, 14.2 ± 0.4 vs. 14.4 ± 1.5 g at 1 month (P = NS), 21.5 ± 0.8 vs. 33.7 ± 0.7 g at 3 months (P < 0.0005), and 25.7 ± 0.7 vs. 36.2 ± 2 g at 5 months (P < 0.0001)]. B, Values represent the mean ± SEM for 5 animals/group. Differences between POMC genotypes are not significant (ob/ob vs. lean littermates: fed, P < 0.0005; fasted, P < 0.001). C, Values represent the mean ± SEM for 5 animals/group. Fasting glucose levels were not significantly different (no supplement vs. corticosterone supplement for 4 months: wild-type, 114 ± 3 vs. 102 ± 5 mg/dl; mutant, 123 ± 7 vs. 109 ± 5 mg/dl).
Results

**Homozygous POMC-null mutants have normal insulin and fasted glucose levels, and only slightly elevated fed glucose levels**

Blood samples of male and female POMC mice of all three genotypes were analyzed for glucose at 1, 3, and 5 months of age (Fig. 1A). Male and female mice were bled either at noon with food ad libitum (fed) or in the morning after a 15-h fast (fasted). Fasted glucose levels were indistinguishable between mutant and wild-type littermates at all ages. Fed glucose levels were indistinguishable between mice of all genotypes at 1 month of age and were slightly, but significantly, higher in homozygous POMC-null mutants at 3- and 5-month-old mutants vs. wild types. Thus, the slightly elevated fed glucose levels correlate with increased body weight, as body weights of mutants and wild types are not significantly different at 1 month of age, but are significantly higher in homozygous mutant mice vs. wild-type mice at 3 and 5 months of age.

We next determined serum insulin levels in fed and fasted adult (5-month-old) POMC wild-type, heterozygous, and homozygous null mice (Fig. 1B). For POMC homozygous and heterozygous mutants of both genders, insulin levels were indistinguishable from those in their wild-type littermates. For comparison, in ob/ob mice (5-month-old females), insulin levels were more than 30 times higher than normal (Fig. 1B).

Corticosterone has an important influence on glucose homeostasis. Homozygous POMC mutant mice do not have any corticosterone due to the absence of adrenal glands and of ACTH. We were interested to determine whether they became hyperglycemic in the presence of corticosterone. Continuous supplementation of corticosterone in the drinking water (25 μg/ml) for more than 4 months did not change overall fasting blood glucose levels in either wild-type or homozygous mutant mice (Fig. 1C).

**Homozygous POMC-null mutants have normal glucose tolerance**

To test glucose homeostasis in POMC wild-type, heterozygous, and homozygous null mice, they were challenged with glucose in an ip glucose tolerance test. Male and female mice, 4–5 months of age, were fasted overnight and then received an ip injection of glucose (3 mg/kg). Glucose measurements were determined from tail blood (Fig. 2). There were no significant differences among the three genotypes in their ability to clear glucose from the bloodstream.

**Homozygous POMC-null mutants have an increased sensitivity to insulin in an ITT**

We next tested the insulin response of POMC wild-type, heterozygous, and homozygous null mice in an ip ITT (Fig. 3). Male and female mice (3.5–5.5 months of age) were fasted overnight and then received an ip injection of insulin (human insulin, 1 U/kg). Blood glucose was measured in tail blood. There was no significant difference among the three genotypes with respect to the ability of the injected insulin to lower blood glucose levels. However, after the lowest level of blood glucose was reached, about 1 h after insulin injection, blood glucose levels were increasing in wild-type and heterozygous mice, whereas in homozygous POMC-null mutant mice, blood glucose levels continued to drop, and the mice unexpectedly died of hypoglycemic shock. The same results were obtained when mice were challenged with insulin after a 5-h fast instead of an overnight fast (data not shown).

**Homozygous POMC-null mutant mice fail to up-regulate glucagon after insulin challenge**

In humans and mice, insulin-induced hypoglycemia causes rapid increases in plasma glucagon and epinephrine levels at the onset of the glucose counterregulatory response; increases in plasma levels of other hormones, including cortisol, occur later in the counterregulatory process (18, 20, 21). Recovery from short-term insulin-induced hypoglycemia is affected little by the lack of epinephrine [for example, bilateral adrenalectomy (22)]. However, the combination of epinephrine deficiency and inhibition of glucagon results in a failure of glucose recovery (23–25). Thus, in the correction of hypoglycemia, glucagon plays a primary role, and epinephrine becomes critical when glucagon is deficient. The homozygous POMC-null mouse mutants lack epinephrine; thus, the failure of these mice to mount a counterregulatory glucose response after insulin challenge could result from a combined deficiency of epinephrine and glucagon. Therefore, we measured the glucagon response after insulin challenge. Mice (males, 3.5–5.5 months of age) were fasted overnight and then received an ip injection of insulin (human insulin, 1 U/kg). Blood was collected retroorbitally once from three to five mice per time point, and serum samples
were analyzed for glucagon (Fig. 4). Wild-type and heterozygous mice showed the typical response after insulin injection, i.e. a sharp increase in serum glucagon within the first 45 min, which then tapered off. Homozygous POMC-null mutant males failed to mount an appropriate glucagon response, in that their serum glucagon levels increased slowly and stayed significantly below wild-type levels at a time when wild-type levels peaked. In addition, even 90 min after insulin injection, when mutant values reached their peak, they remained below the peak observed in wild-type mice. Again, similar results are obtained when mice were fasted for only 5 h; glucagon levels for homozygous mutants could not be determined because they died of hypoglycemic shock between 90–150 min after insulin injection.

**Peripheral MSH, but not ACTH, rescues homozygous POMC-null mutants from hypoglycemia during ITT**

To test whether the presence of corticosterone in homozygous POMC-null mutant mice would change their glucose homeostasis with respect to glucose counterregulation, mice were supplemented with corticosterone in the drinking water (25 μg/ml) for 4 months. ITTs were carried out before and 1 and 4 months after the start of corticosterone treatment. For ITTs, food was removed in the morning from female mice (4.5–5.5 months of age); 5 h later they received an ip injection of insulin (human insulin, 1 U/kg). Blood glucose measurements were made using tail blood. Wild-type mice with corticosterone supplementation showed a slight increase in the glucose rebound after insulin injection (Fig. 6A). In homozygous POMC-null mutant mice, corticosterone treatment prevented hypoglycemic shock after insulin challenge (Fig. 6B); mutant mice showed significantly higher blood glucose levels with corticosterone supplementation than those without supplementation. These blood glucose levels after insulin challenge in homozygous POMC mutants supplemented with corticosterone were indistinguishable from wild-type
levels. Supplementation with corticosterone did not lead to increased glucagon levels in fasted wild-type or homozygous POMC-null mutant mice (data not shown).

MSH and corticosterone both contribute to rescuing homozygous POMC-null mutants from hypoglycemia during ITT

The results presented above show that both administration of MSH analog and corticosterone supplementation prevent hypoglycemia in homozygous POMC-null mutant mice in an ITT. We examined whether these hormones act independently or additively on glucose homeostasis. We tested the effect of combining treatment with MSH analog and corticosterone on the outcome of the ITTs. For ITTs, food was removed in the morning from female mice (4.5–5.5 months of age); 5 h later they received an ip injection of insulin (human insulin, 1 U/kg). Blood glucose measurements were made in tail blood. MSH analog (1 μg/mouse, ip) was injected 1 h before insulin injection or daily once per day for 14 d. Mice were supplemented with corticosterone in the drinking water for 4 wk continuously. ITTs were performed before and 2 or 4 wk after the start of corticosterone supplementation. Data are shown in Fig. 7. A single injection of MSH analog rescued homozygous mutant mice from hypoglycemia after insulin challenge (Fig. 7A). The same effect was achieved after supplementing homozygous mutant mice with corticosterone in the drinking water for 2 wk (Fig. 7B). Although MSH analog and corticosterone individually protect against hypoglycemia, there was no additive effect of a single MSH analog injection in corticosterone-supplemented mice (Fig. 7B) or of continuous injection of MSH analog in corticosterone-supplemented mice (Fig. 7C).

Discussion

Mice lacking POMC, and thus all of the melanocortins and adrenal hormones, are surprisingly well balanced with respect to glucose homeostasis: they have normal serum levels of insulin, normal fasting levels of glucose, and normal clearance of glucose in a glucose tolerance test. Thus, insulin production and sensitivity, and glucose uptake in peripheral tissues are functioning normally. Although there was a very slight increase in glucose levels in the fed state in homozygous POMC-null mutants after they became obese, the most surprising finding was a striking impairment in the counterregulatory glucose response after insulin-induced hypoglycemia.

These results are in remarkable contrast to findings in other models with genetically or pharmacologically induced modifications of central melanocortin signaling only where increased melanocortin signaling leads to insulin sensitivity
and decreased melanocortin signaling leads to insulin resistance. These data are themselves contradictory, however, with some showing short-term action of MSH, and others only showing effects after long-term treatment. Fan et al. (26) observed that homozygous MC4-R-null mice show impaired glucose homeostasis before the onset of obesity; they have increased fasting insulin levels and an increased insulin resistance evidenced by an impaired ITT. Fan et al. (26) further observed that intracerebroventricular (icv) injection of the MSH agonist Ac-[Nle4,Asp5,Phe7,Lys10]-α-MSH4-10-NH2 (MTII) induces plasma insulin levels to fall and fasting glucose levels to rise 1 h after injection in wild-type C57BL/6 mice. Glucose tolerance in these mice was impaired, making an effect of the centrally administered MTII on peripheral insulin release a possible mechanism. This central melanocortin signaling effect on glucose homeostasis was also seen in ob/ob mutant mice. Due to their leptin deficiency, these mice have a decreased melanocortinergic tone, including decreased levels of circulating peripheral MSH (27). However, peripheral administration of an MSH analog to ob/ob mice does not result in changes in insulin or glucose levels measured 1 h later (Hochgeschwender, U., unpublished observations). The results reported by Fan et al. (26) suggest that decreased or absent hypothalamic melanocortin signaling, specifically through MC4-R, leads to pathological increased release of insulin and insulin resistance, eventually leading to diabetes. The tonic inhibitory effect of central melanocortin receptor signaling on insulin secretion is thought to be exerted through the regulation of sympathetic outflow to the pancreas.

Evidence for a long-term role of central melanocortin signaling in glucose homeostasis, specifically on peripheral and hepatic insulin action, was provided by Obici et al. (28) in a rat model system using pancreatic insulin clamp techniques. Continuous icv infusion of αMSH in rats resulted in improved peripheral insulin action, i.e. increased glucose uptake and decreased glucose production. Importantly, icv infusion of the MC4-R/MC3-R antagonist SHU9119 impaired peripheral insulin action, i.e. it decreased glucose uptake and increased glucose production. However, in contrast to the observations of Fan et al. (see above), this effect on glucose homeostasis was only observed after a more prolonged treatment, with antagonist being applied continuously for 7 d (28), whereas acute antagonism of central melanocortin receptors, i.e. antagonist given for 6 h only, did not modify hepatic insulin action (29).

What are the differences in results between these models and the homozygous POMC-null mutant mouse? First, the pharmacological manipulations in wild-type mice and rats are performed in animals that are completely normostatic with respect to their metabolism and glucose homeostasis. Importantly in this context they have normal levels of peripheral MSH and normal levels of adrenal hormones. The ob/ob mice, while showing a similar response to central modulation of melanocortin signaling, do this in a completely different metabolic context: they have hyperinsulinemia, hyperglycemia, hypercorticosteronemia, no leptin, and about half the normal levels of peripheral MSH. Finally, the MC4-R-null mouse specifically lacks hypothalamic MC4-R signaling while having normal levels of adrenal hormones, and MC4-R-null mice do have MSH available for interaction with all other melanocortin receptors, both central and peripheral. In fact, MC4-R mutants might actually have increased levels of peripheral MSH inducing imbalances of glucose homeostasis due to excessive melanocortin signaling in the periphery. This remains to be determined.

The differences between the models described above and homozygous POMC mutant mice concern two important aspects: the lack of adrenal hormones, including corticosterone and epinephrine, and the lack of peripheral MSH signaling. Glucocorticoids have an important role in energy homeostasis (30). The effects of glucocorticoids include stimulation of food intake and insulin secretion as well as antagonizing insulin action (31). Several mouse models of obesity show elevated corticosterone levels, and chronically elevated cortisol in humans causes visceral obesity (32). Glucocorticoids stimulate transcription of hepatic gluconeogenic enzymes and thus play a major role in the enhancement of liver glucose output during starvation or stress (33). In the fed state, glucocorticoids stimulate glycogenolysis. Consequently, glucocorticoid receptor-deficient mice (34) or mice lacking 11β-hydroxysteroid dehydrogenase type 1 (35) resist hyperglycemia during starvation or stress and show elevated liver glycogen in the fed state. Furthermore, removal of glucocorticoids by adrenalectomy improves glucose tolerance in several animal models of obesity (36–39); among the possible
mechanisms are increased glucose uptake by peripheral tissues and decreased hepatic glucose production. Thus, if considered in isolation, the lack of glucocorticoids in homozygous POMC-null mutant mice could explain their normal levels of insulin and glucose as well as their failure of counterregulation in response to insulin-induced hypoglycemia. However, long-term supplementation of homozygous POMC-null mutant mice with corticosterone does not explain their normal levels of insulin and glucose as well as their failure of counterregulation in response to insulin-induced hypoglycemia. Although it does prevent hypoglycemia upon insulin challenge, it does not lead to hyperinsulinemia, as in the homozygous POMC mutant mouse. The relative effects of lack of melanocortins vs. lack of glucocorticoids on body homeostasis and glucose homeostasis remain to be determined.

Interestingly, protection of homozygous POMC mutant mice from their failure of the counterregulatory glucose response in insulin-induced hypoglycemia is achieved by peripheral application of MSH analog, but not ACTH, before the insulin challenge. Although ACTH activates all melanocortin receptors in vitro, this is not the case in vivo under the experimental conditions chosen; injection of ACTH did not have effects comparable to those of the MSH analog in this study or in our previous studies (17, 27). We previously showed that peripheral administration of MSH analog in
homeozygous POMC mutant mice (17) as well as in ob/ob mice (27) leads to a normalization of their pathologically low metabolic rates independent of food intake. Note, however, that in these mutants, MSH only raises the metabolic rate into the normal range, whereas in wild-type mice, MSH does not increase the metabolic rate. Peripherally administered MSH analog does not act centrally, because it does not cross the blood-brain barrier (40, 41). Peripheral injection of MSH analog in homozygous POMC mutant mice does not lead to a change in blood glucose or serum insulin levels per se measured 1 h later. Thus, the peripheral application of MSH does not have the same effects as the central administration of MSH, which increases blood glucose and decreases plasma insulin within 30–60 min in wild-type and ob/ob mice (26).

However, peripheral injection of MSH analog in fasted homozygous POMC-null mice results in a 130% increase in glucagon levels. Glucagon has long been thought to be the primary counterregulatory hormone to insulin, preventing hypoglycemia by increasing hepatic glucose production (42). Glucagon receptor knockout mice partially compensate for the lack of glucagon receptor activation by an increased sensitivity to epinephrine (43). Homozygous POMC-null mutant mice lack epinephrine, and they also have an attenuated glucagon response to insulin challenge, whereas peripheral MSH increases glucagon levels in homozygous POMC-null mutant mice. The mechanistic details of MSH induction of glucagon and its role in the counterregulatory response remain to be determined.

Several decades ago data were presented showing that peripheral application of MSH increases plasma levels of glucagon, insulin, and glucose (44, 45). In mice, hyperglycemia occurred despite a direct effect of MSH on insulin release from the pancreas, excluding interference of MSH with insulin secretion or peripheral action, and it occurred in adrenalectomized mice as well, excluding the influence of adrenal cortex or medulla (44). An observed increased glucose output by the liver due to increased hepatic glycogenolysis led to the hypothesis of a direct action of MSH on pancreatic α cells to release glucagon. Increased glucagon release upon peripheral administration of MSH was indeed later demonstrated in rabbits (45). This increased glucagon output was not inhibited by adrenergic blockers, suggesting a direct action of MSH on the pancreas, rather than a centrally mediated action.

The following quote (46) sums up the concept of central and peripheral effects of POMC peptides on glucose homoeostasis, and although this was written in 1986, it seems to have lost none of its relevance today: “POMC-derived peptides have been demonstrated in many tissues, and may have effects on plasma levels of glucagon, insulin and glucose through several mechanisms. The presence of POMC-derived peptides in the pancreas and their in vitro effects on pancreatic hormone release may suggest direct effects on pancreatic cells. The presence of POMC-derived peptides in the hypothalamus and their central effects on the autonomic nervous system may indicate functions in the central regulation of glucose homeostasis and endocrine pancreas function. It remains to be determined which of the referred effects of the POMC-derived peptides on plasma levels of glucagon, insulin and glucose have physiological significance, and whether or not they may play a pathophysiological role in various diseases.”

By now, sufficient evidence has accumulated that MSH acts both centrally and peripherally to maintain glucose homoeostasis, as it acts both centrally and peripherally to regulate fat metabolism. Our results indicate that peripherally, MSH leads to an increase in insulin resistance, whereas previous work indicated that MSH acting centrally leads to an
increase in insulin sensitivity. This type of reciprocal action, diagrammed schematically in Fig. 8, may be important in maintaining glucose homeostasis. Further, this model provides a number of testable hypotheses that can be followed up in subsequent experiments.

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Address all correspondence and requests for reprints to: Dr. Ute Hochgeschwender, Eleanor Roosevelt Institute, University of Denver, 1899 Gaylord Street, Denver, Colorado 80206. E-mail: uhochgeschwender@omrf.ouhsc.edu. Or to: Dr. Miles B. Brennan, 13th Street, MS 48, Oklahoma City, Oklahoma 73104. E-mail: utebrennan@brenna3@bdus.

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