Hypothalamic AMP-activated protein kinase activation with AICAR amplifies counterregulatory responses to hypoglycemia in a rodent model of type 1 diabetes


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Fan X, Ding Y, Brown S, Zhou L, Shaw M, Vella MC, Cheng H, McNay EC, Sherwin RS, McCrimmon RJ. Hypothalamic AMP-activated protein kinase activation with AICAR amplifies counterregulatory responses to hypoglycemia in a rodent model of type 1 diabetes. Am J Physiol Regul Integr Comp Physiol 296: R1702–R1708, 2009. First published April 8, 2009; doi:10.1152/ajpregu.90600.2008.–In nondiabetic rodents, AMP-activated protein kinase (AMPK) plays a role in the glucose-sensing mechanism used by the ventromedial hypothalamus (VMH), a key brain region involved in the detection of hypoglycemia. However, AMPK is regulated by both hyper- and hypoglycemia, so whether AMPK plays a similar role in type 1 diabetes (T1DM) is unknown. To address this issue, we used four groups of chronically catheterized male diabetic BB rats, a rodent model of autoimmune T1DM with established insulin—requiring diabetes (40 ± 4 pmol/l basal c-peptide). Two groups were subjected to 3 days of recurrent hypoglycemia (RH), while the other two groups were kept hyperglycemic [chronic hyperglycemia (CH)]. All groups subsequently underwent hyperinsulinemic hypoglycemic clamp studies on day 4 in conjunction with VMH microinjection with either saline (control) or AICAR (5-aminoimidazole-4-carboxamide) to activate AMPK. Compared with controls, local VMH application of AICAR during hypoglycemia amplified both glucagon [means ± SE, area under the curve over time (AUC/τ) 144 ± 43 vs. 50 ± 11 ng·1−1·min−1; P < 0.05] and epinephrine [4.27 ± 0.96 vs. 1.06 ± 0.26 nmol·1−1·min−1; P < 0.05] responses in RH-BB rats, and amplified the glucagon [151 ± 22 vs. 85 ± 22 ng·1−1·min−1; P < 0.05] response in CH-BB rats. We conclude that VMH AMPK also plays a role in glucose-sensing during hypoglycemia in a rodent model of T1DM. Moreover, our data suggest that it may be possible to partially restore the hypoglycemia-specific glucagon secretory defect characteristic of T1DM through manipulation of VMH AMPK.

epinephrine; glucagon; ventromedial hypothalamus; adeno-associated viral vector

HYPOGLYCEMIA REMAINS THE MAJOR LIMITING FACTOR TO INTENSIVE INSULIN THERAPY IN TYPE 1 DIABETES (T1DM) (9). INDIVIDUALS WITH T1DM ARE PARTICULARLY PRONE TO HYPOGLYCEMIA BOTH BECAUSE OF THEIR NEED FOR EXOGENOUS AND UNREGULATED INSULIN THERAPY AND BECAUSE OF DEFECTS IN THE NORMAL PHYSIOLOGICAL COUNTERREGULATORY RESPONSE TO ACUTE HYPOGLYCEMIA (29). DEVELOPING THERAPIES TO REDUCE THE FREQUENCY OR SEVERITY OF HYPOGLYCEMIA WILL REQUIRE A GREATER UNDERSTANDING OF THE PHYSIOLOGICAL MECHANISMS UNDERLYING HYPOGLYCEMIA DETECTION AND THE IMPACT OF T1DM ON THESE MECHANISMS.

Falling glucose levels are detected within discrete regions of the brain (3–5, 14, 40), and periphery (11). Of these, the ventromedial hypothalamus (VMH) is thought to play a key role in the detection and integration of hypoglycemia signals and subsequent triggering of a counterregulatory defense response (3–5, 13, 30, 31, 33, 42, 47). Emerging evidence supports a key role for the serine/threonine kinase AMP-activated protein kinase (AMPK) in the sensing of hypoglycemia within the VMH. Local activation of AMPK in the VMH with 5-aminoimidazole-4-carboxamide (AICAR) amplified the glucose counterregulatory response to hypoglycemia in normal Sprague-Dawley rats (31) and reversed impaired hormonal counterregulatory responses in normal rats exposed to recurrent hypoglycemia (RH) (30). Moreover, selective downregulation of AMPK in the VMH using a locally delivered short hairpin RNA significantly suppressed the counterregulatory response to subsequent hypoglycemia (32). This work is supported by others who have shown hypothalamic AMPK is activated in response to fasting or central glucoprivation (24, 26, 34), and, moreover, that intracerebroventricular preadministration of the AMPK inhibitor, compound C, or hypothalamic overexpression of a dominant-negative AMPK suppresses the counterregulatory response to acute hypoglycemia (17).

However, AMPK can also be regulated by chronic exposure to high glucose. Acute hyperglycemia (up to 5 h) can reduce AMPK activation in muscle and liver (25), kidney (27), and heart (23), as well as in incubated muscle (21). AMPK may therefore act bidirectionally, potentially functioning as a feedback mechanism to limit glucose uptake into tissues under conditions of hyperglycemia. This raises the possibility that the fluctuating metabolic state of T1DM, namely intermittent hypo- and hyperglycemia may have a variety of effects on AMPK in the brain, the net effect of which may be that AMPK activation in the VMH in T1DM has little or no effect on counterregulatory responses to acute hypoglycemia. We, therefore, sought to determine whether VMH AMPK activation would amplify counterregulatory responses to hypoglycemia in diabetic BB rats. The diabetic BB rat, a rodent model of autoimmune diabetes, was chosen because, like its human counterpart, it has an absolute requirement for exogenous insulin therapy, develops defective glucagon responses to acute hypoglycemia shortly after disease development (22), and develops defective epinephrine responses following RH (38). These are all hallmarks of human T1DM, which makes this rodent model particularly relevant to individuals with T1DM.

MATERIALS AND METHODS

Animals. Male diabetic BB/Wor rats (Biomedical Research Models, Worcester, MA) with established insulin—requiring diabetes (n = 30; 14–28 days disease duration) and male Sprague-Dawley rats (n =
24) were housed in the Yale Animal Resource Center on a 12:12-h day-night cycle, fed a standard pellet diet (22% protein, 5% fat, and 51% carbohydrate; cat. no. 2018; Harlan, Boston, MA) and maintained on once-daily PZI insulin (BCP Veterinary Pharmacy, Houston, TX). The animal care and experimental protocols were reviewed and approved by the Yale Animal Care and Use Committee.

Rodent surgery. Ten days prior to each study the rats were anesthesitized with an intraperitoneal injection (1 ml/kg) of a mixture of xylazine (20 mg/ml AnaSed; Lloyd Laboratories, Shenandoah, IA) and ketamine (100 mg/ml Ketaset; Aveco, Fort Dodge, IA) in a ratio of 1:2 (vol:vol). The rats initially underwent vascular surgery for the implantation of chronic vascular catheters, as described previously (41). The catheters [PE-50 tubing with a tip made from Silastic laboratory tubing (0.51 mm ID)] are inserted via a neck incision into the internal jugular vein and carotid artery and extended to the level of the right atrium and aortic arch, respectively. They are then tunneled subcutaneously and externalized at the nap of the neck where the catheter ends are left free. Catheter patency is maintained by filling them with a heparin/polyvinylpyrrolidone solution. After catheter insertion, VMH (anterior-posterior, −2.6 mm; medial-lateral ± 3.8 mm; and dorsoventral, 8.3 mm; at an angle of 20 degrees) microinjection guide cannulas were inserted stereotaxically as described previously (4, 5). The coordinates chosen leave the guide cannula tip 1 mm from the VMH and minimizes tissue damage and gliosis in the area of interest. Previous studies have shown that microinjection to the VMH results in relatively little spreadout with the immediate microinjection site (5).

Study 1. In this study, the effect of providing an additional pharmacological stimulus to AMPK in the VMH in chronically hyperglycemic or recurrently hypoglycemia diabetic BB rats was examined. Diabetic BB rats require insulin therapy to prevent ketosis and death. The diabetic rats in our facility are treated with once-daily PZI insulin (BCP Veterinary Pharmacy) injected subcutaneously at 1700 with doses based on body weight, tail vein glucose at 0900, and study protocol. Diabetic BB rats in the present study were divided into two groups; Chronic hyperglycemia (CH) and RH. For the CH group, insulin doses were adjusted pre- and postoperatively to avoid exposure to hypoglycemia and to maintain glucose levels in the moderate-to-low range. The average morning tail vein glucose throughout this pre-study phase for the CH group was 309 ± 14 mg/dl. RH diabetic rats in addition to basal PZI insulin replacement at 1700 received an IP 10 U/kg dose of human regular insulin (Eli Lilly, Indianapolis, IN) at 0900 on the 5 consecutive days prior to surgery. Postoperatively the rats were allowed a 5-day recovery period with moderate glucose control and then underwent a second 5-day period of recurrent once-daily hypoglycemia. During the hypoglycemia period, food was withheld for 3 h to allow for moderate sustained hypoglycemia. At the end of this period the rats were given free access to food. Average tail vein glucose readings for the 5-day preoperative, postoperative, and 5-day pre-study were, respectively, 39 ± 1, 304 ± 18, and 38 ± 2 mg/dl (the readings on the hypoglycemia study days were taken at the end of the 3-h period of hypoglycemia). On the clamp study day, the CH and RH diabetic BB rats were microinjected into the VMH with either AICAR or saline; thus four groups of rats were studied; 1) CH-VMH AICAR (n = 6; 0.1 μl/min for 5 min, total dose 16 ng); 2) CH-VMH control (n = 6; 0.1 μl/min for 5 min); 3) RH-VMH AICAR (n = 6; 0.1 μl/min for 5 min, total dose 16 ng); 4) RH-VMH control (n = 6; 0.1 μl/min for 5 min).

Study 2. In this initial study, we sought to confirm the utility of AICAR (5-aminimidazole-4-carboxamide; Sigma-Aldrich) as an agent for activating AMPK in the VMH. Concerns have arisen with regard to the selectivity of AICAR and, most importantly, the potential for activation of other AMP-regulated kinases and adenosine (15). We have recently shown that selectively downregulating expression levels of the α-catalytic subunit of AMPK through local delivery of an adeno-associated viral vector (AAV) containing a short hair pin RNA for the α-catalytic subunit reduced AMPK gene expression (AMPK-siRNA) in the VMH by ~30–40% and significantly suppressed hormonal counterregulatory responses to hypoglycemia 7–10 days post-AAV microinjection (32). Thus we hypothesized that if AICAR was acting via AMPK, then the AICAR effect should be at least blunted following VMH AMPK downregulation. In this study, normal male Sprague-Dawley rats were microinjected with an AAV containing an AMPK-siRNA (n = 18), or a control RNA (n = 6) as described previously (32). These rats were allowed to recover from surgery and then 10-days later underwent a hyperinsulinemic hypoglycemic clamp study with VMH microinjection under three conditions: 1) control siRNA + VMH saline injection (n = 6), 2) AMPK-siRNA + VMH saline (n = 9), or 3) AMPK-siRNA + VMH AICAR (n = 9), (doses as above).

Hyperinsulinemic hypoglycemic clamp and VMH microinjection protocol. Both normal Sprague-Dawley and diabetic BB rats underwent this protocol. All animals were fasted overnight. On the morning of the study the vascular catheters were opened and the animals were allowed to settle and recover from any stress of handling for at least 2 h. Thirty minutes prior to the hypoglycemia clamp study, 22-gauge microinjection needles, designed to extend 1 mm beyond the tip of the guide cannula (Plastics One, Roanoke, VA), were inserted through the guide cannula bilaterally into each VMH. The study rat was then microinjected over 5 min (0.1 μl/min) with either AICAR (5-aminimidazole-4-carboxamide; Sigma-Aldrich; total dose, 16 ng) dissolved in 0.9% saline or 0.9% saline as a control, as described above. Microinjection was performed in vivo 30 min prior to initiating the hyperinsulinemic hypoglycemic clamp study using a CMA-102 infusion pump (CMA Microdialysis, North Chelmsford, MA). Following microinjection the needles were left in place for 5 min before being removed. Thereafter, a hyperinsulinemic hypoglycemic clamp technique as adapted for the rat (38) was used to provide a standardized hypoglycemic stimulus. At time 0, a 2-h 20 μU·kg⁻¹·min⁻¹ infusion of human regular insulin (Eli Lilly) was begun. The plasma glucose was allowed to fall to ~2.8 mmol/l and was then maintained at this level for 120 min using a variable rate 20% dextrose infusion based on frequent (5–10 min) plasma glucose determinations. Plasma samples for insulin, c-peptide, epinephrine, and glucagon were obtained premicroinjection (t = −30 min), immediately before the clamp procedure (t = 0 min), and during hypoglycemia (t = 60 and 90 or 120 min). At the end of the study, the rats were euthanized and the probe position confirmed in all rats histologically. Only those rats with injection sites confirmed within the VMH (which represented ~70% of studies) were included for analysis.

Analytical procedures. Plasma levels of glucose were measured by the glucose oxidase method (Beckman, Fullerton, CA). Catecholamine analysis was performed by HPLC using electrochemical detection (ESA, Acton, MA); plasma-free insulin, c-peptide, and glucagon were measured by RIA (Linco, Millipore, Billerica, MA). All data are means ± SE, and were analyzed statistically using either a Student’s t-test or repeated-measures ANOVA followed by post hoc testing to localize significant effects as indicated (Prism 4; Graphpad Software, San Diego, CA).

RESULTS

Study 1 (a): VMH AMPK activation in recurrently hypoglycemic diabetic BB rats. Plasma glucose profiles (Fig. 1A) in the two RH animal groups were equivalent and did not differ significantly over the time course of the study [F = 0.3, P = ns (not significant)]. Glucose infusion rates (GIR), however, differed markedly between groups (Fig. 1B), with the RH-control rats requiring significantly more exogenous glucose to maintain the hypoglycemic plateau than RH-AICAR groups (overall F = 43.47, P < .001). Over the last 60 min of the hypoglycemic clamp the mean GIR was 20.2 ± 3.2 vs. 8.0 ± 2.7 mg·kg⁻¹·min⁻¹ for RH-control vs. RH-AICAR, respec-
These data show that RH-control rats required markedly more exogenous glucose to maintain the hypoglycemic control than RH-AICAR injected rats. Plasma levels of insulin rose significantly in both groups during the hypoglycemia clamp studies to levels of $2481 \pm 458$ and $3212 \pm 268$ pmol/l for CH-control vs. CH-AICAR, respectively ($P = ns$). Plasma levels of c-peptide were very low under basal ($42 \pm 6$ vs. $28 \pm 5$ pmol/l, respectively) and hypoglycemic ($37 \pm 4$ vs. $22 \pm 1$ pmol/l, respectively) conditions in these CH-control and CH-AICAR diabetic BB rats, and did not differ significantly between groups.

VMH microinjection had no significant effect on basal levels ($-30$ to $0$ min) of glucagon, epinephrine, and norepinephrine in either CH group, and all hormones rose in response to acute hypoglycemia.

**Study 1 (b): VMH AMPK activation in chronically hyperglycemic diabetic BB rats.** Plasma glucose profiles (Fig. 3A) in the animal groups were similar and did not differ significantly over the time course of the study ($F = 1.3, P = ns$). Mean ± SE plasma glucose during the hypoglycemic plateau ($60-120$ min) was $3.1 \pm 0.1$ vs. $3.3 \pm 0.1$ mmol/l for CH-control vs. CH-AICAR, respectively. Mean glucose infusion rates (GIR) required to maintain the hypoglycemic plateau ($60-120$ min) were slightly, but not significantly reduced in CH-AICAR vs. CH-control BB rats ($1.0 \pm 0.6$ vs. $4.5 \pm 2.0$ mg·kg$^{-1}$·min$^{-1}$; $P = 0.1$; Fig. 3B).

Plasma levels of insulin rose significantly in both groups during the hypoglycemia clamp studies to levels of $2481 \pm 458$ and $3212 \pm 268$ pmol/l for CH-control vs. CH-AICAR, respectively ($P = ns$). Plasma levels of c-peptide were very low under basal ($42 \pm 6$ vs. $28 \pm 5$ pmol/l, respectively) and hypoglycemic ($37 \pm 4$ vs. $22 \pm 1$ pmol/l, respectively) conditions in these CH-control and CH-AICAR diabetic BB rats, and did not differ significantly between groups.

Microinjection had no effect on basal levels ($-30$ to $0$ min) of glucagon, epinephrine, and norepinephrine in either CH group, and all hormones rose in response to acute hypoglycemia.

**Fig. 1.** Plasma glucose (A), glucose infusion rates (GIR; B) during hypoglycemia in RH-control (○) and RH-AICAR (■) groups. Values are means ± SE. *$P < 0.05$ vs. RH-control.

**Fig. 2.** Counterregulatory hormone response to subsequent acute hypoglycemia in RH-control (○) and RH-AICAR (■) groups. Samples for plasma glucagon (A), epinephrine (B), and norepinephrine (C) were taken pre- ($t = -30$ min) and postmicroinjection ($t = 0$ min) of AICAR or control solution and during hyperinsulinemic hypoglycemia ($60$ and $120$ min). Values are means ± SE. *$P < 0.05$ RH-AICAR vs. RH-control.
mia (Fig. 4 A–C). VMH AICAR microinjection significantly amplified glucagon (~80%) (AUC/t 151 ± 22 vs. 85 ± 22 ng·l⁻¹·min⁻¹; CH-AICAR vs. CH-control, respectively; P < 0.05), but not epinephrine (3.25 ± 0.45 vs. 7.00 ± 1.1 nmol·l⁻¹·min⁻¹, respectively; P = 0.2) or norepinephrine (2.36 ± 0.9 vs. 2.00 ± 0.50 nmol·l⁻¹·min⁻¹, respectively; P = 0.07) responses to the hypoglycemia challenge.

Study 2: effect of VMH AICAR during hypoglycemia in normal rats following selective AMPK downregulation. To control for potential nonspecific effects of AICAR, initial studies were performed in normal Sprague-Dawley rats previously microinjected to the VMH with either a short-hairpin RNA designed to selectively downregulate AMPK (VMH AMPK-siRNA VMH saline or VMH AMPK-siRNA VMH AICAR groups) or a control short-hairpin RNA (VMH control-siRNA VMH saline). Compared with the control siRNA study, and consistent with our previous work (32), VMH AMPK downregulation through local delivery of the AMPK siRNA led to a significant reduction in the glucagon (~40%), epinephrine (~30%), and norepinephrine (~30%) responses to acute hypoglycemia (Fig. 5). This effect was not significantly reversed by microinjection of AICAR to the VMH (Fig. 5; P = ns for all hormones), a finding which supports the use of AICAR in subsequent studies in the BB rat as an activator of AMPK.

DISCUSSION

Perhaps the most noteworthy finding in the present study was the demonstration that VMH AMPK activation in both RH- and CH-diabetic BB rats produced a significant increase in the glucagon response (~80–180%) to subsequent hypoglycemia. The inability of individuals with T1DM to produce a substantial rise in plasma glucagon in response to a falling glucose is a major reason for their increased predisposition to severe hypoglycemia (10, 16). The α-cell is subject to both local pancreatic and distal (neural and circulating humoral) influences, because it has proven extremely difficult to determine the principal mechanistic defect(s) that are responsible for impaired glucagon-secretory responses to hypoglycemia in T1DM.

One major factor leading to the development of defective glucagon secretion in T1DM is thought to be the failure of intraislet insulin levels to fall (“switch-off”) during acute hypoglycemia (2, 28, 43). In support of this, restoring the intraislet insulin switch-off signal during hypoglycemia is sufficient to restore glucagon secretion in vitro using perfused islets from streptozotocin-treated Wistar rats (20), and in vivo, albeit in anesthetized rats, using an intrapancreatic artery...
infusion of insulin that was abruptly discontinued when streptozotocin-treated Wistar rats (48) and diabetic BB rats (49) became hypoglycemic. However, there remain a number of neural pathways that may also contribute to the development of defective glucagon counterregulation in T1DM and that might, if sufficiently activated, restore glucagon secretory responses to hypoglycemia. The pancreatic α-cell has an extensive and complex autonomic innervation [reviewed in detail in Tabor-sky et al. (44)] with considerable redundancy. All three of the autonomic inputs to the α-cell, epinephrine, sympathetic, and parasympathetic innervation, are capable of stimulating glucagon secretion (44), and autonomic blockade in rodents (18) and primates (19) significantly impairs glucagon secretion during hypoglycemia.

In the present study, we demonstrate that microinjection of the pharmacological AMPK activator, AICAR, increases the magnitude of the glucagon secretory response in both CH- and RH-diabetic BB rats. This finding is consistent with a number of other studies in nondiabetic rodents demonstrating that VMH manipu-

lution may modulate the glucagon secretory response to acute hypoglycemia (e.g., Refs. 30 and 31). We have recently also shown that mice that are unable to secrete glutamate from steroidogenic factor 1 neurons, which are exclusively expressed in the VMH of rodents, fail to secrete glucagon in response to acute hypoglycemia (45). Taken together, these studies indicate an important role for the VMH in the regulation of glucagon secretion in both nondiabetic and diabetic rodents. Retrograde tracer studies in rodent models using pseudorabies virus suggest that this occurs via the autonomic nervous system, with transynaptic transmission of the pseudorabies virus reaching the pancreas initially by way of the paraventricular nucleus and zona incerta, and subsequently by either the intermediolateral column of the spinal cord (sympathetic) or dorsal motor nucleus of the vagus (parasympathetic) (6). Our study does not enable us to determine the role of the VMH in the development of defective glucagon secretion to hypoglycemia in T1DM, or the relative primacy of a β-cell-mediated vs. a central defect, but is does suggest that the secretory defect may be at least partially reversed through an intervention designed to augment VMH glucose-sensing.

It is intriguing that a similar effect of VMH AICAR on glucagon was seen in both RH- and CH-BB rats, whereas a differential effect was seen on the epinephrine response to hypoglycemia. However, the CH-diabetic BB rats are very insulin resistant and glucose levels during the clamp only fell to ~3.3 mmol/l in CH-diabetic BB rats given VMH-AICAR and ~3.1 mmol/l in CH-diabetic BB controls, which may have been insufficient to reveal differences between the two. In addition, the rise in glucagon seen in both diabetic BB rat groups did not achieve the levels seen in nondiabetic animals. While this may reflect local intraislet influences, it is also of note that catecholamine responses in the BB rat were equally suboptimal, suggesting that other factors relating to the diabetic state contribute to defective counterregulation.

It is important to examine the relevance of our rodent model to the human condition. The diabetic BB rat develops autoimmune-mediated β-cell destruction, which leads to a ketosis-prone, insulin-dependent diabetic state that is very similar, although more aggressive in the speed of its development, to human T1DM (37). In vivo studies also demonstrate a hypoglycemia-specific defect in glucagon secretion (22), as well as the development of defective hormonal counterregulation following RH (38). These are also characteristics of the human condition (9). In the present study, a small, albeit nonsignificant, rise in glucagon was seen during hypoglycemia in the diabetic BB rat control studies. In contrast, in studies of individuals with T1DM the glucagon response to hypoglycemia is often absent. This difference may reflect the shorter duration of disease in the diabetic BB rats studied (2–4 wk), which means some of the BB rats (~20% of control animals in the present study) may not have completely lost their α-cell response to hypoglycemia. A relationship between increasing disease duration and the development of defective glucagon counterregulation is seen in human subjects with T1DM (35). It is also noteworthy that subjects with T1DM do not all demonstrate a complete absence of glucagon secretion during hypoglycemia (35).

We also considered the possibility that AICAR might act independently of AMPK through locally induced changes in non-AMPK-mediated pathways or through other AMP-regu-
AMPK activation during hypoglycemia

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