Hypoglycemic detection at the portal vein is mediated by capsaicin-sensitive primary sensory neurons

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Fujita S, Bohland MA, Sanchez-Watts G, Watts AG, Donovan CM. Hypoglycemic detection at the portal vein is mediated by capsaicin-sensitive primary sensory neurons. Am J Physiol Endocrinol Metab 293: E96–E101, 2007. First published March 20, 2007; doi:10.1152/ajpendo.00415.2006.—To elucidate the type of spinal afferent involved in hypoglycemic detection at the portal vein, we considered the potential role of capsaicin-sensitive primary sensory neurons. Specifically, we examined the effect of capsaicin-induced ablation of portal vein afferents on the sympathoadrenal response to hypoglycemia. Under anesthesia, the portal vein was isolated in rats and either capsaicin (CAP) or the vehicle (CON) solution applied topically. During the same surgery, the carotid artery (sampling) and jugular vein (infusion) were cannulated. One week later, all animals underwent a hyperinsulinemic hypoglycemic clamp, with glucose (variable) and insulin (25 mU·kg⁻¹·min⁻¹) infused via the jugular vein. Systemic hypoglycemia (2.76 ± 0.05 mM) was induced by minute 75 and sustained until minute 105. By design, no significant differences were observed in arterial glucose or insulin concentrations between groups. When hypoglycemia was induced in CON, the plasma epinephrine concentration increased from 0.67 ± 0.05 nM at basal to 36.15 ± 2.32 nM by minute 105. Compared with CON, CAP animals demonstrated an 80% suppression in epinephrine levels by minute 105, 7.11 ± 0.55 nM (P < 0.001). A similar response to hypoglycemia was observed for norepinephrine, with CAP values suppressed by 48% compared with CON. Immunohistochemical analysis of the portal vein revealed an 85% decrease in the number of calcitonin gene-related peptide-reactive nerve fibers following capsaicin-induced ablation. That the suppression in the sympathoadrenal response was comparable to our previous findings for total denervation of the portal vein indicates that hypoglycemic detection at the portal vein is mediated by capsaicin-sensitive primary sensory neurons.

calcitonin gene-related peptide; sympathoadrenal response; glucose sensing

GLUCOSE SENSORS LOCATED IN THE PORTAL VEIN ARE NOW RECOGNIZED AS IMPORTANT MODULATORS OF THE SYMPATHOADRENALE RESPONSE TO HYPOGLYCEMIA. MASKING THESE SENSORS VIA LOCAL GLUCOSE INFUSION, I.E., NORMALIZING PORTAL VEIN GLYCEMIA, IN THE PRESENCE OF SYSTEMIC HYPOGLYCEMIA HAS BEEN SHOWN TO SUBSTANTIALLY SUPPRESS THE SYMPATHETIC RESPONSE (9, 10, 13, 14). TOTAL DENERVATION OF THE PORTAL VEIN VIA TOPICAL APPLICATION OF PHENOL YIELDS A SIMILAR DIMINISHED SYMPATHOADRENALE RESPONSE TO SYSTEMIC HYPOGLYCEMIA (15), INDICATING A CRITICAL ROLE FOR PORTAL VEIN AFFERENTS IN GLYCEMIC DETECTION. GLUCOSE-SENSITIVE AFFERENTS ARE KNOWN TO RESIDE IN THE HEPATIC VAGUS (22, 23), BUT RECENT STUDIES SUGGEST THAT THESE VAGAL AFFERENTS ARE NOT INVOLVED IN HYPOGLYCEMIC DETECTION AS IT RELATES TO NEURAL-HORMONAL COUNTERREGULATION (17, 18). IN CONTRAST, CELIAC SUPERIOR MESENTERIC GANGLIONECTOMY (CSMG), WHICH INTERRUPTS THE SPINAL AXIS, HAS BEEN SHOWN TO SUPPRESS THE SYMPATHOADRENALE RESPONSE TO HYPOGLYCEMIA (11).

THAT HYPOGLYCEMIC DETECTION AT THE PORTAL VEIN APPEARS MEDIATED BY SPINAL AFFERENTS SUGGESTS THAT THESE GLUCOSE SENSORS MAY BE CAPSAICIN-SENSITIVE PRIMARY SENSORY NEURONS (CPSN). CALCITONIN GENE-RELATED PEPTIDE (CGRP) IS RECOGNIZED AS A RELIABLE MARKER FOR THE DORSAL ROOT SENSORY NEURONS AND THEIR DISTRIBUTION WITHIN VARIOUS TISSUES (4). THE PORTAL VEIN HAS BEEN SHOWN TO BE EXTENSIVELY INNERVATED BY CGRP FIBERS AS WELL AS NEURONS EXPRESSING SUBSTANCE P (SP) (2, 3). VANILLOID RECEPTORS, WHICH BIND CAPSAICIN, COLocalize WITH SENSORY NEURONS EXPRESSING BOTH CGRP AND SP (28). PORTAL VEIN IMMUNOREACTIVITY FOR BOTH CGRP AND SP IS SUBSTANTIALLY SUPPRESSED BY SYSTEMIC CAPSAICIN PRETREATMENT IN NEONATAL RATS, A PROCEDURE THAT INDUCES PERMANENT DEGENERATION OF CPSNs. CSMG, BUT NOT VAGOTOMY, ALSO SUPPRESSES CGRP IMMUNOREACTIVITY WITHIN THE PORTAL VEIN (12). AS WITH CSMG, SYSTEMIC CAPSAICIN PRETREATMENT OF NEONATES ALSO IMPAIRS THE SYMPATHOADRENALE RESPONSE TO INSULIN-INDUCED HYPOGLYCEMIA (1, 8).

IN CONTRAST TO THE WIDESPREAD DESTRUCTION OF CPSNs CHARACTERISTIC OF SYSTEMIC PRETREATMENT WITH CAPSAICIN, TOPICAL APPLICATION OF CAPSAICIN DIRECTLY ON A NERVE OR INNERVATED TISSUE IS AN EFFECTIVE MEANS OF PERMANENTLY IMPAIRING CPSN FUNCTION WITHIN A SPECIFIC LOCAL AREA (6, 20). IN THE PRESENT STUDY, WE EMPLOYED THIS APPROACH TO SELECTIVELY IMPAIR CPSNs IN THE PORTAL VEIN. ANIMALS WERE THEN EXPOSED TO A HYPERINSULINEMIC HYPOGLYCEMIC CLAMP TO ASCERTAIN THE POSSIBLE ROLE OF CAPSAICIN-SENSITIVE FIBERS IN MEDIATING THE SYMPATHOADRENALE RESPONSE.

METHODS

Experiments were conducted on male Wistar rats (n = 10) in the conscious relaxed state. All surgical and experimental procedures were preapproved by the University of Southern California Institutional Animal Care and Use Committee.

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Experimental procedures. One week prior to experiments, animals were chronically cannulated under single-dose anesthesia (3:3:1 ketamine HCl-xylazine-acepromazine maleate; 0.10 ml/100 g body wt) given intramuscularly. Cannulas were placed in the carotid artery (Clay Adams, PE-50) for arterial blood sampling and in the jugular vein (dual cannula Silastic, 0.03 mm ID) for peripheral infusions of insulin and glucose. At the time of cannulation, experimental animals underwent permanent desensitization of portal CPSNs via topical capsaicin application (CAP). A laparotomy was performed, the portal

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vein isolated, and small cotton swabs soaked in a 1% capsaicin solution (vehicle solution: 10% ethanol, 10% Tween 80 in 0.9% saline) applied topically. Adjacent tissues were covered with gauze and parafilm to prevent any contact with the capsaicin-soaked swabs. Cotton swabs were removed after 15 min, and the portal vein was rinsed thoroughly with normal saline. Control animals (CON) underwent identical surgical procedures but with cotton swabs soaked in the vehicle solution alone. All cannulas were tunneled subcutaneously and exteriorized at the back of the neck and all wounds closed via individual sutures. Cannulas were connected to a dual-channel swivel via a tethering system (Instech Laboratories, Plymouth Meeting, PA), and animals were allowed 6 days of recovery to regain body weight. Following recovery, body weights for CON, 235 ± 15 g, and CAP, 241 ± 16 g, were not significantly different.

Twenty-four hours prior to the experiment, all food was removed from the cage. On the day of the experiment, jugular catheter extensions from the dual-channel infusion swivel were connected to infusion pumps for insulin and glucose. Animals were then allowed 30 min of rest prior to initiating sampling (~60 to ~30 min). Basal arterial samples were drawn via the carotid cannula at ~30 and 0 min for analysis of glucose, insulin, and catecholamines. At minute 0, insulin (25 mU•kg⁻¹•min⁻¹) and glucose infusions (variable) were initiated and maintained for 105 min. The glucose infusion (GINF) was decreased slowly over time so as to achieve deep hypoglycemia, 2.76 ± 0.05 mM, by minute 75 and thereafter adjusted to maintain this level through minute 105. Arterial plasma samples were drawn at 60, 75, 90, and 105 min for catecholamine analysis, with an additional sample drawn at minute 105 for insulin. Sampled blood was replaced with donor blood over the course of the experiment.

To confirm that the efferent aspect of the sympathoadrenal response remained intact in rats subjected to capsaicin treatment, glucopenia was induced by 2-deoxyglucose (2-DG) injection. Experiments were conducted on a separate group of male Wistar rats (weight 243 ± 22 g, n = 10) in the conscious relaxed state. One week prior to experiments, animals underwent surgical procedures identical to those above but without jugular cannulation. Animals were allowed 6 days of recovery. Twenty-four hours prior to the experiment all food was removed. On the day of the experiment, the animal was allowed 30 min (~60 to ~30 min) to acclimate. Basal samples were then drawn at ~30 and 0 min for analysis of glucose and catecholamines. At minute 0, a single dose of 2-DG (500 mg/kg dissolved in 0.5 ml saline) was injected. Serial arterial sampling for glucose was performed every 10 min for the next 60 min, with sampling for catecholamines at 15, 30, 45, and 60 min. Additional samples were drawn at minutes 0 and 60 for measurement of insulin concentration.

**Immunohistochemical verification.** A separate group of CON (n = 6) and CAP (n = 5) animals underwent surgical and denervation procedures identical to those described above. Seven days following the surgery, animals were anesthetized (2,2,2-tribromoethanol), transcardially perfused with paraformaldehyde (4%), and the portal vein removed and stored for immunohistochemical analysis of CGRP reactivity. Whole mount sections of the portal veins (~0.5 cm) were brought to room temperature and passed through six 5-min rinses of Tris-buffered saline (TBS; 0.1 M Tris buffer containing 0.9% saline, pH 7.4). Sections were then placed in a blocking solution for 2 h at room temperature [2% normal donkey serum (NDS), 0.1% Triton, diluted in TBS], followed by six more rinses with TBS. Sections were then reacted for 48 h at 4°C with a mouse monoclonal anti-CGRP antibody (no. 4901, CURE Digestive Diseases Research Center Antibody Core) diluted in TBS (with 2% NDS, 0.25% Triton) to a final concentration of 1:1000. Following washes with TBS, sections were incubated with a biotinylated goat anti-mouse antibody (no. 111-035-144, Jackson ImmunoResearch Laboratories, West Grove, PA) and then with horseradish peroxidase-conjugated avidin-biotin complex (no. 111-035-144, Vector Laboratories, Burlingame, CA). Following washes with TBS, reactions were visualized with diaminobenzidine tetrahydrochloride (Sigma-Aldrich, St. Louis, MO) followed by counterstaining with hematoxylin (Sigma-Aldrich).

**Fig. 1.** Photographs of portal vein sections reacted with calcitonin gene-related peptide (CGRP) monoclonal antibody from control (CON; A) and capsaicin-treated (CAP; B) animals. **C:** no. of CGRP-reactive fibers per sample area are expressed as means ± SE. Significant difference between CAP and CON (P = 0.0015).
concentration of 1:12K. To amplify the reaction, sections were subsequently rinsed in TBS (6 times) then reacted with a donkey-anti mouse IgG (H+L) conjugated to CY3 (Jackson ImmunoResearch Laboratories, no. 715-165-150) diluted to 1:500 for an additional 24 h. Following a final series of washes with TBS, sections were mounted, on slides, air dried, and coverslipped with a mounting medium (Vectashield) for fluorescence microscopy. The immunoreactive sections were then digitally photographed with a camera fitted on a bright-field microscope [Nikon Microphot SA light microscope fitted with a Spot RT Color digital camera (Diagnostics Instruments), using SPOT Image v. 3.5.5 for Mac OS]. The extent of innervation was quantified by counting all visible CGRP-reactive fibers within randomly selected sample field views (92 × 80 μm).

Analytic procedures. Glucose was assayed via the glucose oxidase method utilizing a fixed enzyme analyzer (YSI, Yellow Springs, OH). Epinephrine and norepinephrine concentrations were assayed using a single-isotope radioenzymatic approach (24). Insulin samples were assayed via RIA utilizing a commercially available kit (Linco Research, St. Charles, MO).

Data analysis. The results are expressed as means ± SE. Comparisons of animal characteristics between groups were made using an ANOVA for independent groups. Comparisons between treatments over time were made by repeated-measures ANOVA using Tukey’s test for post hoc analysis. In all cases the significance was set at P < 0.05.

RESULTS

Capsaicin-induced denervation. Immunohistochemical analysis revealed an extensive mesh-like network of CGRP-reactive fibers in portal veins taken from control animals (Fig. 1). However, 7 days following the topical application of a capsaicin solution, CGRP reactivity was substantially decreased. Following the application of capsaicin, the number of CGRP-reactive fibers per sample area declined from 27.5 ± 4.6 to 4.2 ± 1.2 in the portal vein (P = 0.0015).

Insulin-induced hypoglycemia. Basal values for plasma insulin, 22.01 ± 8.12 and 27.44 ± 9.80 μU/ml, and glucose concentration, 6.20 ± 0.13 and 6.29 ± 0.11 mM (CAP and CON, respectively), were not significantly different between groups. Insulin infusion, initiated at minute 0, elevated the plasma insulin concentration to 990 ± 124 U/ml for CAP and 788 ± 165 μU/ml for CON [P = nonsignificant (NS)]. During insulin infusion, arterial glucose fell from a basal value of 6.29 ± 0.11 mM to a nadir of 2.76 ± 0.05 mM in CON by minute 75, which was maintained to minute 105. By design, arterial glucose was matched between groups over the course of the experiment, with no significant difference observed at any time point (Fig. 2). Mean G_INF was elevated for CAP compared with CON, but this failed to reach significance. For the hypoglycemic period (60–105 min), total G_INF was 463 ± 43 vs. 412 ± 39 μmol/100 g (P = 0.2) for CAP and CON, respectively.

Basal epinephrine, 0.78 ± 0.12 and 0.67 ± 0.06 nM, and norepinephrine, 2.34 ± 0.30 and 2.02 ± 0.19 nM (CAP and CON, respectively), values were not significantly different between groups (Fig. 3). In response to hypoglycemia, epinephrine values for CON increased throughout the experiment, reaching a peak value of 36.15 ± 2.32 nM by minute 105. In contrast, the epinephrine response in CAP animals peaked at minute 90 (9.99 ± 3.45 nM) and by minute 105 was suppressed by 80% compared with CON, 7.11 ± 0.55 vs. 36.15 ± 2.32

Fig. 2. Data are expressed as means ± SE for arterial glucose concentration at basal (−30 to 0 min) and during hyperinsulinemic hypoglycemic clamp (0–105 min) for CON and CAP animals.

Fig. 3. Epinephrine (A) and norepinephrine (B) concentrations at basal (−30 to 0 min) and during sustained deep hypoglycemia (60–105 min) for CON and CAP animals, expressed as means ± SE. *Significant difference between CAP and CON (P < 0.05).
nM, respectively ($P < 0.001$). Norepinephrine demonstrated a similar pattern, increasing 4.7-fold above basal (9.51 ± 0.74 nM) in CON animals, whereas CAP reached peak values of only 4.99 ± 0.64 nM, 48% less than CON ($P < 0.01$).

**Sympathoadrenal response to 2-DG-induced glucopenia.** Basal glucose concentrations, 6.23 ± 0.16 and 6.63 ± 0.26 mM for CAP and CON, respectively, were not significantly different between groups. In response to the 2-DG injection, glucose concentration rose throughout the experiment, reaching maximum values of 22.52 ± 0.74 and 24.96 ± 0.48 mM by minute 60 for CAP and CON, respectively (Fig. 4). No significant differences in glucose concentration were observed between CAP and CON at any time during the experiment. Insulin concentrations were not significantly different between groups either at basal, 20.35 ± 4.99 and 17.17 ± 4.18 μU/ml, or following 2-DG injection, 16.98 ± 5.12 and 18.09 ± 9.42 μU/ml for CAP and CON, respectively.

Basal epinephrine concentrations were not significantly different between groups, 1.24 ± 0.32 vs. 1.21 ± 0.24 nM for CAP and CON, respectively (Fig. 5). Plasma epinephrine concentrations increased following the 2-DG injection, with peak values of 44.73 ± 6.50 and 42.51 ± 6.84 nM for CAP and CON, respectively ($P = NS$). Basal norepinephrine concentrations were not significantly different between groups, 2.97 ± 0.28 and 2.34 ± 0.37 nM for CAP and CON, respectively. Norepinephrine concentrations rose significantly in both groups following the 2-DG injection reaching peak values of 12.10 ± 0.88 and 10.53 ± 1.87 nM for CAP and CON, respectively ($P = NS$).

**DISCUSSION**

CPSNs are known to subserve a variety of visceral sensory functions, including nociception, mechanosensitivity, osmoreception, and chemosensitivity (6, 28). The present findings extend the role of CPSNs to hypoglycemic detection at the portal vein as it relates to hypoglycemic counterregulation. When the portal vein was pretreated with capsaicin 7 days prior to the experiment, animals demonstrated an 80% suppression in the epinephrine and a 48% suppression in the norepinephrine response to hypoglycemia. Consistent with this, we observed an 86% decrease in the number of CGRP-reactive fibers in the portal veins from capsaicin-treated animals. Since the catecholamine response to 2-DG-induced central glucopenia was not affected by capsaicin treatment and was comparable to that for insulin-induced hypoglycemia in control animals, the observed results could not be attributed to a diminished efferent sympathoadrenal capacity in CAP animals. Thus, the blunted catecholamine response observed in CAP animals was due to a defect in afferent signaling from portal vein glucose sensors.

Topical application of capsaicin either directly on the nerve (6) or in innervated tissue (20) is known to result in the functional impairment of primary sensory neurons expressing vanillloid receptors. In the periphery, these are primarily unmyelinated C-fibers, which are small in diameter and peptidergic (28). They employ a number of sensory neuropeptides, including SP, CGRP, somatostatin, and galanin. In the portahepatis, expression of SP and CGRP is largely restricted to the
portal vein and hepatic artery, with little appearing in the parenchyma (12, 27). Substance P containing fibers are found in both the adventitial and medial plexus of the portal vein (2, 3). Functional impairment of these neurons via capsaicin, while not completely understood, is associated with the depletion of these sensory neuropeptides and an inability to restore their levels (28). In the present study, we observed a substantial depletion of CGRP-reactive nerve fibers in the portal vein from animals treated topically with capsaicin (Fig. 1). Animals treated with capsaicin demonstrated a concomitant reduction in the sympathoadrenal response to hypoglycemia, i.e., a reduced ability to detect hypoglycemia. As CGRP is a marker of spinal afferent innervation (4), current results are consistent with our previous report demonstrating a significant suppression in the sympathoadrenal response to systemic hypoglycemia for animals undergoing CSMG, but not those subjected to subdiaphragmatic vagotomy (11). Interestingly, both CSMG and topical applications of capsaicin to the celiac ganglion have been shown to lead to a depletion of CGRP and SP in the portal vein, whereas subdiaphragmatic vagotomy has little impact (12, 25). The current findings lend support to the concept that hypoglycemic detection at the portal vein is mediated by unmyelinated C-fibers originating for the dorsal root ganglia.

Hypoglycemia-associated autonomic failure (HAAF) in which antecedent hypoglycemia leads to a diminished sympathoadrenal response, is now recognized as a primary limitation in the effective treatment of type 1 diabetes (7). Although the pathogenesis underlying HAAF is unknown, several hypotheses have been put forward implicating impaired glucose sensing in the central nervous system (CNS) (7). However, the possibility that peripheral sensory neurons might be involved remains an intriguing possibility. Diabetic peripheral neuropathy (DPN) is among the most widespread chronic complications affecting the diabetic patient population (16). Perceived to result from years of hyperglycemia, DPN is now known to manifest itself very early in the progression of the disease. Indeed, a less severe, but identical, form of DPN, known as impaired glucose tolerance neuropathy (IGTN), presents in the prediabetic state (16). Primary among the peripheral sensory neurons impacted by IGTN are the unmyelinated C-fibers, i.e., the same type that appears to mediate hypoglycemic detection at the portal vein. Along with hyperglycemia, prolonged or repeated bouts of hypoglycemia can also result in peripheral neuropathy. In humans this manifests itself primarily as a distal sensory polyneuropathy, which may result from hypoglycemia-induced neuronal hyperperfusion and hypoxia (19). The cell bodies and long peripheral axons of dorsal root ganglia sensory neurons reside outside the blood-CNS barrier. As such, they are exposed to larger and more rapid changes in their metabolic environment compared with neurons of the CNS (21). We have identified spinal sensory neurons as mediators of hypoglycemic detection at the portal vein and the subsequent sympathoadrenal response (11). Given the known susceptibility of these sensory neurons to various glycemic insults, they may constitute an important element in the pathogenesis of HAAF.

In the current study, 2-DG was employed to test the integrity of the effector aspect of the sympathoadrenal response, i.e., adrenal output, following capsaicin treatment. A large single bolus of 2-DG can induce rapid CNS glucopenia and a sympathoadrenal response of equal or greater magnitude than that observed for insulin-induced hypoglycemia (5, 29). Although 2-DG administered intravenously undoubtedly affects other glucose-sensing tissues, the impact on sympathetic output appears to be dominated by glucopenia at the CNS. That the sympathoadrenal response to 2-DG was not impaired in CAP animals was not surprising. In an earlier report, we noted that portal glucose sensing appears to dominate hypoglycemic detection when the fall in glycemia is slow (10). That is, suppressing the sympathoadrenal response by normalizing portal vein glycemia during systemic hypoglycemia was substantially more effective when hypoglycemia developed over 200 min (10) vs. only 30 min (9, 13). Thus, when the fall in glycemia was rapid, hypoglycemic detection appeared to shift away from the portal vein toward the brain. The rapid sympathoadrenal response to 2-DG observed in the present study is indicative of rapid central glucopenia that may supersede any input from the periphery. The similar 2-DG-induced sympathoadrenal responses for both CON and CAP animals, comparable in magnitude to the insulin-induced response for CON animals, clearly demonstrate that the capacity for a maximal sympathoadrenal response was not compromised by capsaicin treatment. Thus, the differences observed in the current study for insulin-induced hypoglycemia must be attributable to an impaired glucose sensing in capsaicin treated animals.

CPSNs have previously been implicated in hypoglycemic counterregulation, although results have been mixed. Most studies report a suppressed epinephrine response to hypoglycemia in rats pretreated with capsaicin as neonates (1). However, Zhou et al. (30) reported enhanced release of catecholamines during hypoglycemia in animals pretreated with capsaicin. In all cases, interpretation of these findings is confounded by the fact that systemic neonatal capsaicin pretreatment effectively denervates all CPSNs in the body and may have an impact on other cells expressing vanilloid receptors (6, 26, 28). Ritter and Dinh (26) reported widespread neural degeneration in the brains of animals treated systemically with capsaicin as neonates. Among those regions affected were the nucleus of the solitary tract, area postrema, and ventromedial hypothalamus, all purported to be involved in hypoglycemic detection. The present study avoided this problem by employing topical capsaicin, thereby restricting the impairment of CPSNs to the portal vein and greatly simplifying interpretation of the results; i.e., the suppressed sympathoadrenal response to hypoglycemia develops as a result of impaired CPSNs at the portal vein. Furthermore, comparing the present results with our earlier findings for total denervation (15) and celiac-superior mesenteric ganglionectomy (11) suggests that hypoglycemic detection at the portal vein is mediated entirely by capsaicin-sensitive primary sensory neurons that are spinal in origin.

REFERENCES

HYPOGLYCEMIC DETECTION AT THE PORTAL VEIN


