Calcitonin Gene–Related Peptide and Induction of Hyperglycemia in Conscious Rats In Vivo

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The effect of calcitonin gene–related peptide (CGRP) on glucose metabolism was investigated in conscious and unrestrained rats in vivo. Intravenous injection of rat CGRP (5.67 and 0.567 nmol/kg) caused a significant, dose-dependent increase in plasma glucose concentration and a simultaneous dose-dependent increase in plasma insulin level. In contrast, plasma glucagon level was not changed. On the other hand, intravenous infusion of CGRP (46.6 pmol · kg^{-1} · min^{-1}) decreased tolerance to intragastric administration of glucose (IGGTT). Plasma insulin response to IGGTT, however, was not affected by CGRP infusion. Moreover, although intravenous injection of CGRP (5.67 nmol/kg) elicited a significant increase in plasma epinephrine and norepinephrine concentrations, concomitant administration of epinephrine and norepinephrine, inducing a more prominent rise in plasma catecholamines than those induced by CGRP, affected neither plasma glucose nor insulin levels. Finally, plasma insulin levels obtained by simulating CGRP-induced changes in plasma glucose or glucose plus catecholamine levels by infusion of glucose or glucose plus catecholamines were not different from those induced by CGRP injection. These results suggest that CGRP has a hyperglycemic action that is not mediated by sympathetic outflow in conscious rats, and inhibition of insulin secretion, if any, does not play a major role in this hyperglycemic action of CGRP. We have demonstrated specific CGRP receptors linked to adenylate cyclase activation in rat liver plasma membranes; this hyperglycemic effect of CGRP in vivo may be partly due to its direct action on the liver. *Diabetes* 39:168–74, 1990

Calcium	1 mM = 4 mg/dl		Glucose	1 mM = 18 mg/dl	
Epinephrine	1 pM = 0.183 pg/ml		Insulin	1 pM = 0.167 μU/ml	
Glucagon	1 ng/L = 1 pg/ml		Norepinephrine	1 nM = 169 pg/ml	

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Calcitonin gene–related peptide (CGRP), a 37–amino acid polypeptide, is produced by alternative tissue-specific RNA processing of the calcitonin gene (1). Studies have revealed the presence of a significant amount of CGRP not only in the gastrointestinal tract (2) but also in the endocrine pancreas (2,3), suggesting a role for CGRP in glucose metabolism.

Indeed, in addition to various biological actions such as vasodilation (4), stimulation of amylase release from exocrine pancreas (5), stimulation of gastric somatostatin release (6), and inhibition of gastric acid secretion (7), CGRP has been shown to increase blood glucose levels in association with inhibition of insulin secretion in mice (3) and pigs (8) in vivo. Moreover, an in vitro study with isolated islets has also indicated a direct inhibitory action of CGRP on insulin release from β-cells, suggesting the possible involvement of inhibition of insulin release in the hyperglycemic action of CGRP (9). In a human study, however, CGRP changed neither blood glucose nor plasma insulin levels (10). In addition, CGRP has been shown to augment hyperglycemic response to terbutaline (a β_2-adrenergic agonist) without affecting insulin secretion in pigs (8). Thus, it is still unclear whether the suppression of insulin secretion is mainly responsible for the hyperglycemic action of CGRP.

We recently demonstrated that CGRP at physiological concentrations stimulates adenylate cyclase activity via specific receptors in rat liver plasma membranes and postulated that CGRP may modulate glucose metabolism in the liver (11). In this study, therefore, to elucidate the mechanism responsible for the action of CGRP on glucose metabolism in vivo, the effect of exogenous CGRP on the levels of not only plasma glucose but also plasma pancreatic hormones and catecholamines were examined in conscious unrestrained rats.

RESEARCH DESIGN AND METHODS

ANIMALS AND SURGICAL PROCEDURES

Adult male Sprague-Dawley rats weighing 300–350 g were used throughout this study. To perform the experiments under unanesthetized and unrestrained conditions, intravenous and intragastric catheters were implanted into all the animals for infusion of test substances and blood sampling and intragastric administration of glucose (IGGTT), respectively.

After an overnight fast, a sterile silicone catheter (Silastic 602-155, 1.19 mm OD, 0.64 mm ID; Dow Corning, Midland, MI) was inserted into the right atrium via an incision in the right external jugular vein under pentobarbital sodium anesthesia (37 mg/kg body wt) as described previously (12). Next, an intragastric catheter for glucose administration was implanted into the animals used in experiment 2. After a median laparotomy, the stomach was carefully exposed, and two concentric loops were made with ligatures on the forestomach wall. A hole was then opened with a pair of scissors at the center of the looped ligatures, and a polyethylene catheter (PE-100 tubing, 1.52 mm OD, 0.86 mm ID; Clay Adams, Becton Dickinson, Parsippany, NJ) was inserted into the gastric lumen and held firmly in place by tightening the two ligatures. A small hole was then made in the abdominal wall through which the intragastric catheter was threaded to lead out of the abdominal cavity, and four ligatures were inserted between the inner abdominal wall and the gastric wall and tied tightly around the catheter. These procedures were performed to prevent any leakage of gastric juice into the abdominal cavity after surgery. The abdominal cavity was then closed in two layers. In the last step, a device to immobilize the two catheters was made on the head of the rat. A longitudinal median incision of the skin was made, and the skull was exposed. Then the free ends of the intragastric and the intravenous catheters were run subcutaneously through the head incision and connected to other PE-100 tubes 4 cm long with 20-gauge steel connectors. The whole assembly was anchored at the steel connectors to the skull with dental cement (Repairsin, G-C Dental Industrial, Tokyo). The operation was finished by closure of the abdominal and cervical skin, and the open ends of the tubes on the head were kept closed with steel plugs.

After the operation, the animals were housed individually in an air-conditioned room (22 ± 2°C) under standard lighting conditions (12 h artificial light/day from 0600 to 1800) and given free access to laboratory chow (Oriental Yeast, Tokyo) and tap water ad libitum. The intravenous catheter was flushed with heparinized saline every day. About 2 wk after the operation, animals with body weight that had returned to the preoperative level were used in the experiments after an overnight fast.

EXPERIMENTAL PROTOCOL

In all experiments, the intragastric and intravenous catheters attached to the head of each rat were connected to syringes containing glucose solution and heparinized saline, respectively, through the extension tubing (~30 cm long) at least 1 h before the experiments. The animals were then placed individually in a box that enabled them to move freely. The extension tubings were led out through a hole in the ceiling of the box. Under these conditions, the following experiments were carried out.

Experiment 1. Synthetic rat CGRP (5.67 or 0.567 nmol/ml; Peninsula, Belmont, CA) was dissolved in 1 ml saline, and test animals received an intravenous injection of 5.67 or 0.567 nmol CGRP/kg body wt over 1 min. Control animals were injected with the same volume of saline alone. Blood samples (0.7 ml) were taken through the intravenous catheter immediately before and 5, 15, 30, 45, 60, 90, and 120 min after injection of CGRP.

Experiment 2. Synthetic rat CGRP was dissolved in saline to give a concentration of 233 pmol/ml and then infused at a rate of 0.2 ml · kg^{-1} · min^{-1} (46.6 pmol · kg^{-1} · min^{-1}) through the intravenous catheter with a peristaltic pump (Miniplus 2, Gilson, Villiers, Le Bel, France). Control animals received the same volume of saline at the same rate (0.2 ml · kg^{-1} · min^{-1}). In the next step, D-glucose was dissolved in distilled water to give a concentration of 600 mg/ml, and 2.5 ml/kg body wt of this solution (1.5 g/kg glucose) was administered intragastrically (IGGTT) 5 min after the start of CGRP infusion. Blood samples were collected through the intravenous catheter 5 min before the CGRP infusion and again immediately before and 15, 30, 45, 60, 90, and 120 min after IGGTT. The infusion of CGRP was continued until the last blood sampling.

Experiment 3. A mixed saline solution containing 0.05 μg/ml (−)-epinephrine and 0.25 μg/ml (−)-norepinephrine (Sigma, St. Louis, MO) was injected for 1 min via the intravenous catheter (0.05 and 0.25 μg/kg, respectively). Control animals were injected with the same volume of saline alone. Blood samples were withdrawn immediately before and 5, 10, 15, and 30 min after administration of catecholamines.

Experiment 4. To simulate the effects of CGRP injection on blood glucose and plasma catecholamine levels, D-glucose was dissolved in saline with or without epinephrine plus norepinephrine and infused at a rate of 0.2 ml · kg^{-1} · min^{-1} (glucose, 1 mg · kg^{-1} · min^{-1}; epinephrine, 0.01 μg · kg^{-1} · min^{-1}; norepinephrine, 0.05 μg · kg^{-1} · min^{-1}) for 30 min. Blood samples were taken immediately before and 15, 30, and 45 min after the start of infusion.

Blood samples from these experiments were rapidly transferred to chilled microfuge tubes containing aprotinin (final concn 1000 U/ml) and immediately centrifuged. Plasma was then removed and stored at −40°C until assay, and erythrocytes were resuspended in saline and returned to the rats just after the next sampling to avoid anemia.

MEASUREMENT OF PLASMA GLUCOSE, Ca^{2+}, INSULIN, GLUCAGON, AND CATECHOLAMINES

Plasma glucose levels were determined with a glucose oxidase method, and plasma Ca^{2+} levels were measured by the OCPC method with a Raba Super System (Chugai Pharmaceutical, Tokyo). Plasma insulin levels were measured by polyethylene glycol radioimmunoassay with rat insulin as standard (13), and plasma glucagon was assayed by the talc-absorption method (14) with 30K (purchased from the Diabetes Research Fund, Univ. of Texas Southwestern, Dallas) as antiserum. Plasma catecholamines (epinephrine and norepinephrine) were determined by radioenzymatic assay (15). All values were expressed as means ± SE, and statistical analysis was done with Student's *t* test when two means were compared. When more than two means were compared against a control group, as in experiment 1, the data were

examined by analysis of variance, and then Duncan's new multiple-range test was applied to each of the points (16).

RESULTS

Experiment 1. Mean ± SE basal levels of plasma glucose, insulin, and glucagon in the test group were 5.67 ± 0.13 mM, 61.8 ± 11.7 pM, and 40.2 ± 7.4 ng/L, respectively, whereas those of the control group were 5.41 ± 0.18 mM, 66.8 ± 10.0 pM, and 46.6 ± 8.2 ng/L. Furthermore, the basal values in the control group did not change significantly throughout the experiment. A single intravenous injection of 0.567 or 5.67 nmol/kg rat CGRP elicited a significant increase in plasma glucose concentration, with a peak value of 6.53 ± 0.15 mM ($P < 0.01$ vs. controls) or 8.73 ± 0.28 mM ($P < 0.01$) obtained 15 and 30 min after the injection, respectively. These elevated values of plasma glucose then decreased gradually. This rise in plasma glucose was associated with a significant increase in plasma insulin concentration. The peak values of 143.6 ± 20.0 pM ($P < 0.01$) and 238.8 ± 35.1 pM ($P < 0.01$) plasma insulin were observed 45 and 30 min after CGRP (0.567 and 5.67 nmol/kg) injection, respectively (Fig. 1). The incremental effect of CGRP on plasma glucose and insulin concentrations was therefore dose dependent. In contrast, CGRP induced no remarkable change in plasma glucagon level throughout the experiment (Fig. 1). On the other hand, CGRP (5.67 nmol/kg) also provoked a slight but significant rise in the levels of plasma epinephrine and norepinephrine, with peak values of 2.02 ± 0.12 nM ($P < 0.01$ vs. basal) and 7.74 ± 1.26 nM ($P < 0.05$ vs. basal) at 15 min after injection, respectively, followed by a gradual decrease (Table 1). In addition, plasma Ca^{2+} concentration was decreased significantly only at 30 min after an intravenous injection of 5.67 nmol/kg CGRP ($P < 0.01$), whereas it did not change throughout the experiment in the control group, as shown in Table 2.

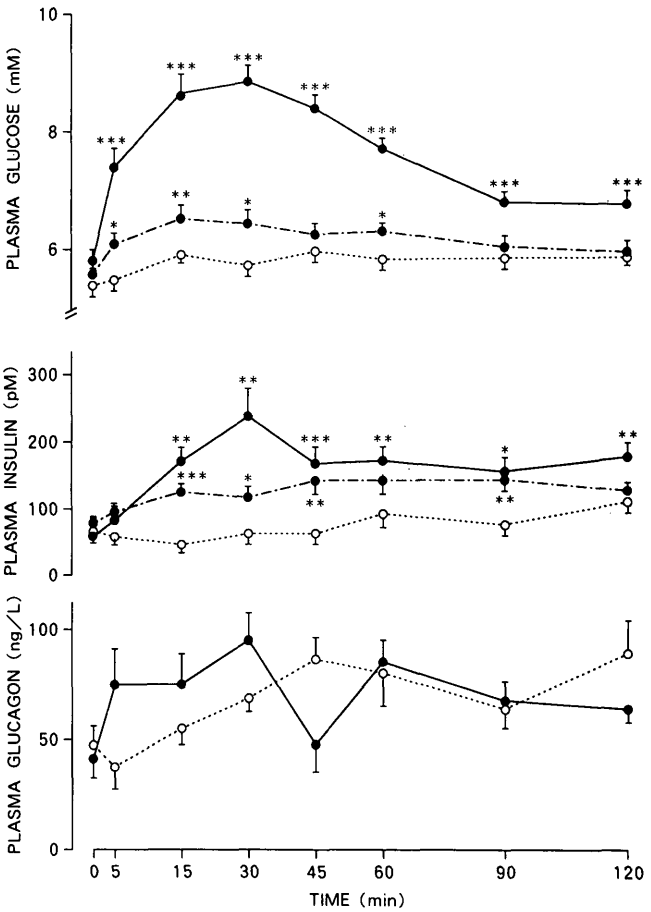

FIG. 1. Effect of intravenous injection of 5.67 (●, *solid lines*) or 0.567 (●, *broken lines*) nmol/kg rat calcitonin gene–related peptide on plasma glucose, insulin, and glucagon levels in conscious rats. ○, Saline alone (controls). Values are means ± SE of 8 experiments. F = 29.14, 8.41, and 2.57 for plasma glucose, insulin, and glucagon, respectively. ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$, vs. controls.

Experiment 2. In the control group, plasma glucose and insulin levels immediately before IGGTT (5 min after start of saline infusion) were 5.43 ± 0.22 mM and 50.1 ± 6.7 pM, respectively, which were not significantly different from those of the test group (glucose, 5.85 ± 0.24 mM; insulin, 80.2 ± 15.0 pM). After IGGTT, the levels of both plasma glucose and insulin in the control group increased to peak values of 9.36 ± 0.39 mM and 948.6 ± 123.6 pM at 15 min, respectively, followed by a gradual decrease. During the intravenous infusion of CGRP (46.6 pmol · kg^{-1} · min^{-1}), IGGTT evoked a more prominent increase in the plasma glucose level than that without CGRP infusion, with a peak value of 11.16 ± 0.35 mM ($P < 0.001$ vs. control) 30 min after IGGTT, and a higher level of plasma glucose lasted until the end of the experiment (Fig. 2). On the other hand, although there was no significant difference between the two groups

TABLE 1
Effects of intravenous injection of 5.67 nmol/kg calcitonin gene–related peptide (CGRP) and 0.05 μg/kg epinephrine plus 0.25 μg/kg norepinephrine on plasma catecholamine levels

	CGRP (nM)		Epinephrine + norepinephrine (nM)	
Time (min)	Epinephrine	Norepinephrine	Epinephrine	Norepinephrine
0	1.03 ± 0.08	3.80 ± 0.95	0.92 ± 0.22	4.07 ± 0.27
15	2.02 ± 0.20*	7.74 ± 1.26†	13.09 ± 2.17*§	64.53 ± 9.04*‡
30	1.72 ± 0.12*	6.61 ± 0.83†	9.25 ± 1.55*‡	48.36 ± 5.23*‡
45	1.51 ± 0.16†	5.46 ± 0.63†	4.89 ± 0.96*‡	29.18 ± 2.21*‡

CGRP or epinephrine plus norepinephrine was injected over 1 min into rats. Values are means ± SE. n = 8 and 4 for CGRP and catecholamines, respectively. F = 36.89 and 66.31 for plasma epinephrine and norepinephrine, respectively.
*$P < 0.01$, †$P < 0.05$, vs. respective basal values.
‡$P < 0.01$, §$P < 0.05$, vs. respective values with CGRP injection.

TABLE 2
Changes in plasma Ca^{2+} levels produced by intravenous injection of 5.67 nmol/kg calcitonin gene–related peptide (CGRP)

	Time postinjection (min)					
	0	5	15	30	60	120
Saline (mM)	2.05 ± 0.05	2.08 ± 0.08	2.09 ± 0.02	2.09 ± 0.03	2.03 ± 0.05	2.08 ± 0.02
CGRP (mM)	2.06 ± 0.05	2.05 ± 0.07	2.08 ± 0.06	1.94 ± 0.04*	2.06 ± 0.05	2.08 ± 0.06

Values are means ± SE from 8 experiments. $F = 2.85$.
*$P < 0.01$ vs. saline (control).

throughout the experiment, recovery of the elevated plasma insulin concentration to the basal level after IGGTT appeared to be delayed during CGRP infusion (Fig. 2). In addition, an intravenous infusion of CGRP (46.6 pmol · kg^{-1} · min^{-1}) produced a significant decrease in the plasma Ca^{2+} concentration only at 60 min after IGGTT ($P < 0.05$ vs. control), whereas a saline infusion had no effect (Table 3).

Experiment 3. As demonstrated in experiment 1, CGRP significantly stimulated catecholamine release (Table 1). Thus, to rule out the possibility that the rise in plasma glucose produced by CGRP was mediated by catecholamine release, we exogenously administered epinephrine and norepinephrine simultaneously. After an intravenous injection of this mixed solution of epinephrine and norepinephrine, plasma epinephrine and norepinephrine levels dramatically rose to 13.09 ± 2.17 and 64.53 ± 9.04 nM at 15 min, respectively (Table 1). However, neither the level of plasma glucose nor that of insulin changed throughout the experiment (Fig. 3).

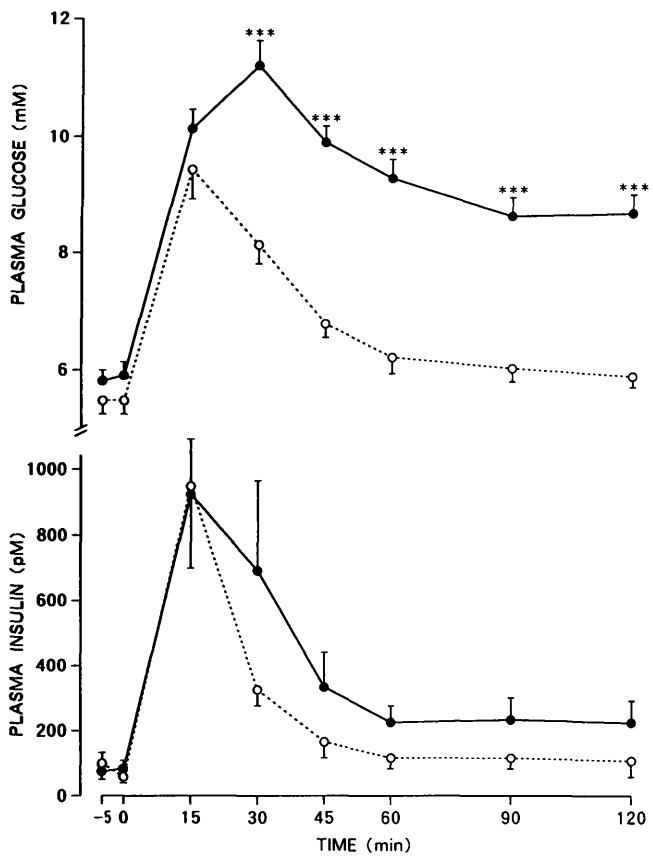

FIG. 2. Effect of intravenous infusion of 46.6 pmol · kg^{-1} · min^{-1} calcitonin gene–related peptide (●) on plasma glucose and insulin levels during intragastric administration of glucose in rats. Control experiment was performed with saline infusion (○). D-Glucose (1.5 g/kg) was administered intragastrically as indicated. Values are means ± SE of 8 experiments. $F = 46.31$ and 9.36 for plasma glucose and insulin, respectively. ***$P < 0.001$ vs. controls.

Experiment 4. As shown in experiment 1, the increase in plasma glucose levels produced by CGRP injection was associated with an increase of plasma insulin and an elevation of plasma catecholamine (Fig. 1; Table 1). Therefore, to examine whether CGRP has a simultaneous inhibitory effect on insulin secretion stimulated by CGRP-induced hyperglycemia and, if so, whether the effects of CGRP on insulin secretion are secondary to increases in the levels of circulating epinephrine and norepinephrine, we simulated the CGRP-induced changes in plasma glucose and catecholamine levels by infusing glucose with or without epinephrine plus norepinephrine. During infusion of glucose (1 mg · kg^{-1} · min^{-1}) with or without catecholamines, plasma glucose levels increased to 8.95 ± 0.26 and 9.01 ± 0.36 mM 30 and 15 min after the start of infusion, respectively, and there were no significant differences in plasma glucose levels among the three groups throughout the experiment (Fig. 4). On the other hand, on simultaneous infusion of glucose and epinephrine plus norepinephrine, plasma epinephrine and norepinephrine levels increased to 3.35 ± 0.57 and 11.05 ± 1.08 nM at 15 min, respectively, both being slightly but significantly higher than those elicited by CGRP injection, and the catecholamine levels remained elevated throughout the infusion period (Fig. 4). In contrast, infusion of glucose alone had no effect on plasma catecholamine levels. However, despite these simulated plasma glucose and catecholamine levels and the difference in plasma catecholamine concentrations, there were no significant differences in plasma insulin levels among these three groups throughout the experiment (Fig. 4).

DISCUSSION

This study clearly demonstrated that rat CGRP not only increased the basal plasma glucose concentration but also enhanced the rise in glucose level after IGGTT in conscious rats, confirming the previous report by Petterson et al. (3), who demonstrated augmentation of baseline plasma glucose levels after intravenous administration of CGRP in conscious mice. Dunning and Taborsky (17) also observed a tendency for basal glucose to increase during intravenous infusion of CGRP in anesthetized dogs. Moreover, Ahren et al. (8) reported marked augmentation of the terbutaline-induced increase in plasma glucose in anesthetized pigs.

TABLE 3
Changes in plasma Ca^{2+} levels produced by intravenous infusion of 46.6 pmol · kg^{-1} · min^{-1} calcitonin gene–related peptide (CGRP) during intragastric administration of glucose (IGGTT)

	Time after IGGTT (min)			
	−5	30	60	120
Saline (mM)	2.16 ± 0.02	2.18 ± 0.04	2.08 ± 0.02	2.07 ± 0.06
CGRP (mM)	2.18 ± 0.03	2.08 ± 0.04	1.91 ± 0.06*	1.89 ± 0.08

Values are means ± SE from 8 experiments. $F = 5.59$.
*$P < 0.05$ vs. saline (control).

Thus, it appears almost certain that CGRP has a hyperglycemic action.

Of particular note in this study, however, was the fact that in addition to the glucose rise, intravenous injection of CGRP elicited a significant dose-dependent increase in plasma insulin concentration. These results are in marked contrast with the previous reports. Indeed, Petterson et al. (3) demonstrated that the CGRP-induced increase in basal glucose was associated with a significant decrease in plasma insulin concentration in conscious mice. Ahren et al. (8) also showed a decrease of basal and glucose-stimulated insulin secretion in response to intrapancreatic infusion of CGRP in anesthetized pigs. Furthermore, with isolated rat pancreatic islets, Ishizuka et al. (9) observed a direct inhibitory action of CGRP on insulin release within the islets. All of these reports suggest that CGRP-induced hyperglycemia may be due to decreased insulin secretion. In contrast to these data, it is clear from our experiment that the suppression of insulin secretion is not a major factor for CGRP-induced hyperglycemia; rather, CGRP may have a direct stimulatory effect on insulin release in conscious rats. However, the significant increase of plasma insulin produced by CGRP infusion was preceded by a significant rise in plasma glucose concentration. Moreover, although CGRP infusion did not alter the peak plasma insulin value during IGGTT, it appeared to delay the subsequent return of plasma insulin to the basal level, in association with prolonged hyperglycemia. Therefore, it seems more likely that CGRP primarily induces hyperglycemia, which in turn causes hyperinsulinemia as a secondary phenomenon. However, CGRP may actually exert a slight insulin-inhibiting action that is masked by the insulin release induced by hyperglycemia. Indeed, the observation that there was no augmented secretion of insulin despite the CGRP-induced glucose response to IGGTT may lend support to this possibility.

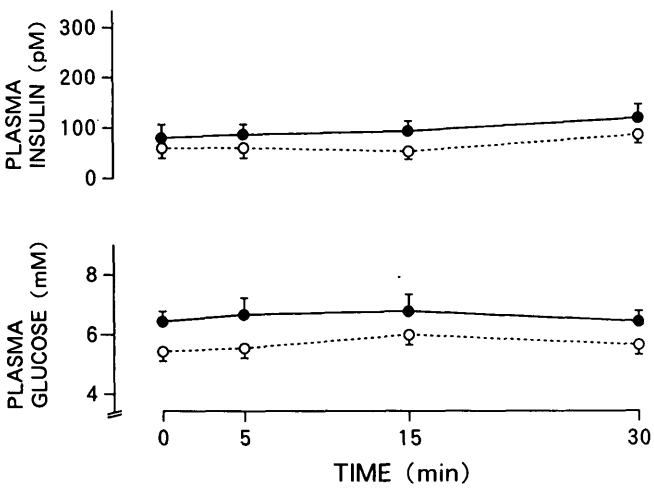

FIG. 3. Time course of plasma glucose and insulin levels before and after concomitant intravenous injection of 0.05 μg/kg epinephrine and 0.25 μg/kg norepinephrine (●) in rats. Control experiment was performed by same volume of saline injection (○). Values are means ± SE of 4 experiments.

Therefore, to examine whether CGRP actually exerts an inhibitory effect on insulin release, we simulated the plasma glucose response to CGRP injection by infusing glucose and found that the insulin response to this glucose infusion was not higher than that induced by CGRP injection. Furthermore, concomitant administration of epinephrine plus norepinephrine with glucose, producing only slightly but significantly higher concentrations of plasma epinephrine and norepinephrine than those obtained by CGRP infusion (thus simulating both the plasma glucose and catecholamine responses to CGRP), induced insulin responses similar to those after CGRP injection or glucose infusion alone. Thus, the involvement of increased plasma catecholamines in the CGRP-induced changes in plasma insulin concentration was ruled out. It appears that CGRP did not exert any inhibitory effect on insulin secretion in our in vivo experiments. The reason for these discrepancies between the results of these experiments and those of others remains unclear, although it could be due to differences in species, the doses administered, or the experimental conditions (i.e., the use or nonuse of anesthesia).

What factors are involved in the hyperglycemic action of CGRP? To answer this question, we observed the responses of plasma glucagon and catecholamines to exogenous CGRP because these substances are major physiological factors possessing hyperglycemic activity. Indeed, Ahren et al. (8) have already reported that the terbutaline-induced glucagon output was potentiated by CGRP in anesthetized pigs. In this study, however, plasma glucagon levels were not responsible for the CGRP-induced hyperglycemia. In contrast to glucagon, intravenous injection of CGRP provoked a significant rise in the concentrations of plasma epinephrine and norepinephrine in conscious rats. These results are in good agreement with the report by Fisher et al. (18), who demonstrated an elevation of plasma norepinephrine concentration on intravenous injection of CGRP in anesthetized rats, and might suggest a role for these elevated plasma catecholamines in CGRP-induced hypergly-

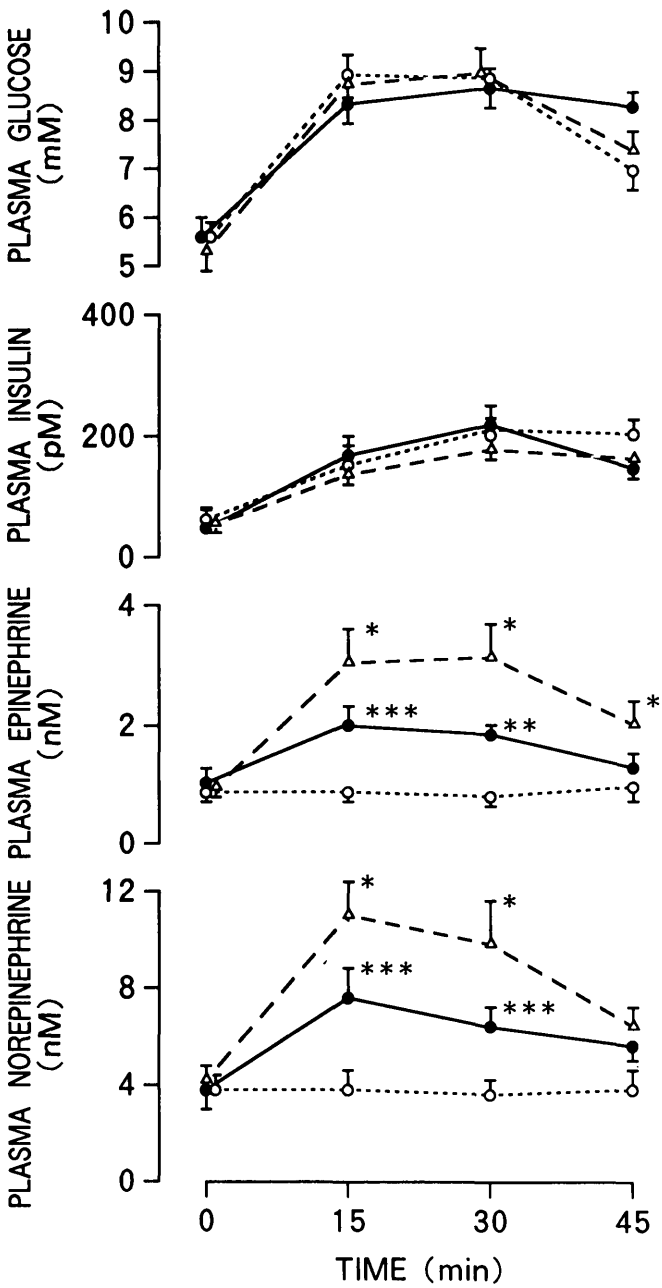

FIG. 4. Effects of intravenous injection of 5.67 nmol/kg calcitonin gene-related peptide (CGRP; ●) and intravenous infusion of glucose (1 mg · kg^{-1} · min^{-1}) with or without epinephrine (0.01 μg · kg^{-1} · min^{-1}) plus norepinephrine (0.05 μg · kg^{-1} · min^{-1}) on plasma glucose, insulin, and catecholamine levels in rats. CGRP (1 ml) was injected over 1 min (n = 8), and glucose solution with (△; n = 6) or without (○; n = 6) catecholamines was infused for 30 min at rate of 0.2 ml · kg^{-1} · min^{-1}. Values are means ± SE. F = 9.99, 57.27, 60.9, and 55.32 for plasma glucose, insulin, epinephrine, and norepinephrine, respectively. ***P < 0.01, **P < 0.05, vs. controls. *P < 0.05 vs. CGRP alone.

cemia. However, we also examined the effects of exogenous administration of catecholamines, which induced significantly higher concentrations of plasma catecholamines than those induced by CGRP, and found that this increase of plasma catecholamines had no effect on the level of plasma glucose or insulin, thus ruling out any involvement of sympathetic outflow in the hyperglycemic action of CGRP. On the other hand, CGRP, like calcitonin, is known to have a hypocalcemic action (19), and changes in plasma Ca^{2+} levels have been reported to affect glucose metabolism (20). Thus, the hyperglycemic action of CGRP may involve changes in plasma Ca^{2+} levels. However, this seems unlikely because CGRP produced only a small and transient decrease in plasma Ca^{2+} levels, and this decrease was observed only after the rise in plasma glucose in response to CGRP. We were thus unable to find any factor that might mediate the hyperglycemic effect of CGRP, raising the possibility of a direct hyperglycemic action of CGRP. In a recent study, on the other hand, specific receptors for CGRP in rat liver plasma membranes were identified (21), and it was subsequently revealed that like glucagon receptors, these receptors are linked to adenylate cyclase activation via stimulatory guanine nucleotide–binding protein (11). Accordingly, because glucagon is known to stimulate glucose production and inhibit glucose utilization via a cyclic AMP–dependent process in the liver (22), it is tempting to speculate that CGRP also induces hyperglycemia, at least partly, by acting on the liver through its specific receptors, although we have not examined the direct effect of CGRP on glucose metabolism in the liver.

Studies have demonstrated a significant amount of CGRP throughout the gastrointestinal tract (2), and CGRP levels in the portal vein are clearly higher than those in peripheral veins in rats (unpublished observations). Thus, it may be reasonable to consider that CGRP released from the gut accumulates in portal blood and acts on the liver to modulate glucose metabolism under physiological conditions. In this experiment, however, we used a large dose of CGRP, which probably induced a supraphysiological plasma concentration of CGRP. Therefore, the question of whether endogenous CGRP is involved in glucose metabolism under physiological conditions remains to be elucidated.

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