

Adrenergic modulation of insulin secretion in response to portal glucose and arginine in the rat

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It has been suggested that there are hepatic receptors for sodium chloride ¹⁾, glucose ^{2,3)}, amino acids ⁴⁻⁷⁾, and osmotic pressure ⁸⁾. Several studies have shown that the receptors for glucose or arginine in the hepato-portal system exert a reflex regulation of the pancreatic neuroendocrine system and modulate insulin secretion ^{2,4-6,9)}. The vagal efferent pathways may be involved in the pancreatic neuroendocrine system via the afferent pathways from the hepatic neural metabolic receptors. Thus, hepatic glucose receptor is suggested to stimulate insulin secretion ²⁾ and hepatic arginine receptor is suggested to inhibit insulin secretion via cholinergic mechanisms ^{4,6)}. However, the neural modulation of hepato-portal glucose-or arginine-receptors in insulin secretion remains to be fully elucidated. In order to clarify this issue, the effect of cholinergic blockade or adrenergic blockade on insulin secretion in response to intraportal glucose or arginine was investigated in the rat.

MATERIALS AND METHODS

Animals

Male Wistar albino rats weighing approximately 250g were provided in this study. After an overnight fasting, the rats were anesthetized with intraperitoneal pentobarbital sodium (30 mg/kg), and the body temperature of the rat was maintained at 37°C on the hot plate throughout the study. Thirty minutes after the abdomen was opened, the following examinations were performed.

Glucose infusion test

To obtain similar levels of arterial blood glucose, glucose in a 20% solution was bolus infused into the femoral vein at a dose of 0.5g/kg (peripheral stimulation) or into the portal vein at a dose of 0.6g/kg (portal stimulation). The blood specimen for blood glucose measurement (0.1ml) was drawn from the abdominal aorta and the blood specimen for insulin measurement (0.5ml) was drawn from the portal vein at 0, 2, 5, and 10 min. In one series of glucose infusion tests, two rats were used to avoid the influence of hypovolemia. Blood specimens were drawn from one rat at 0 and 5, and from the other rat at 2 and 10 min.

Arginine infusion test

Arginine (0.5g/kg in a 10% L-arginine solution) was bolus infused into the femoral vein (peripheral stimulation) or portal vein (portal stimulation), and the blood specimen for blood glucose measurement was drawn from the abdominal aorta and the blood specimen for insulin

measurement was drawn from the portal vein at 0, 5, and 10 min.

Preadministration of atropine, propranolol, or atenolol

Atropine sulphate (1mg/kg, Tanabe Seiyaku, Osaka, Japan), propranolol hydrochloride (0.5mg/kg, ICI Pharma, Osaka, Japan), or atenolol hydrochloride (50mg/kg, Sigma Chemical Co., Missouri, AZ) was administered subcutaneously 30min before the glucose or arginine infusion test.

Measurements

Blood glucose concentration was measured by a glucose oxidase method. Plasma insulin was assayed by radioimmunoassay using rat insulin standard, of which sensitivity was estimated to be $2 \mu\text{U/ml}$. Intra- and interassay coefficients of variation were 5 and 10%.

Statistics of data

The data were expressed as the mean \pm SD. Analysis of variance and two-tailed Student's non-paired *t* test were applied.

RESULTS

Glucose infusion test

As shown in Fig. 1, arterial blood glucose level and portal plasma insulin concentration were not significantly different between peripheral stimulation and portal stimulation.

Arginine infusion test

As shown in Fig. 2, blood glucose level and plasma insulin concentration were not significantly different between peripheral stimulation and portal stimulation.

Glucose infusion test after treatment with blockades

As shown in Figs. 3, 4, and 5, blood glucose responses were not significantly changed by the preadministration of any blockade. In atropine- or atenolol-treated rats, insulin concentration was almost similar in peripheral and portal stimulation (Figs. 3 and 5). In propranolol-treated rats, insulin concentration was significantly ($p < 0.05$) higher in portal stimulation (78 ± 26 and $115 \pm 25 \mu\text{U/ml}$) than in peripheral stimulation (48 ± 13 and $46 \pm 14 \mu\text{U/ml}$) at 5 and 10 min, respectively (Fig. 4).

Arginine infusion test after treatment with blockades

As shown in Figs. 6, 7, and 8, blood glucose responses were not significantly changed by the preadministration of any blockade. In atropine-treated rats, insulin concentration was almost similar in peripheral and portal stimulation (Fig. 6). In propranolol-treated rats, insulin concentrations in portal stimulation (124 ± 50 and $121 \pm 47 \mu\text{U/ml}$) were significantly ($p < 0.05$) higher than those in peripheral stimulation (60 ± 20 and $25 \pm 5 \mu\text{U/ml}$) at 5 and 10 min, respectively (Fig. 7). In atenolol-treated rats, insulin concentration was significantly ($p < 0.05$) higher in portal stimulation ($128 \pm 40 \mu\text{U/ml}$) than in peripheral stimulation ($76 \pm 22 \mu\text{U/ml}$) at 5 min (Fig. 8).

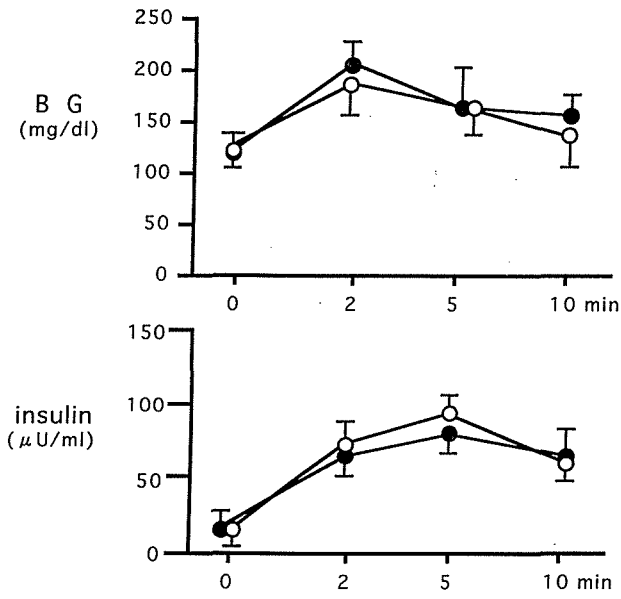


Fig. 1 Blood glucose and plasma insulin responses to glucose
 BG : blood glucose
 ○ portal stimulation, ● peripheral stimulation
 The values are means \pm SD.

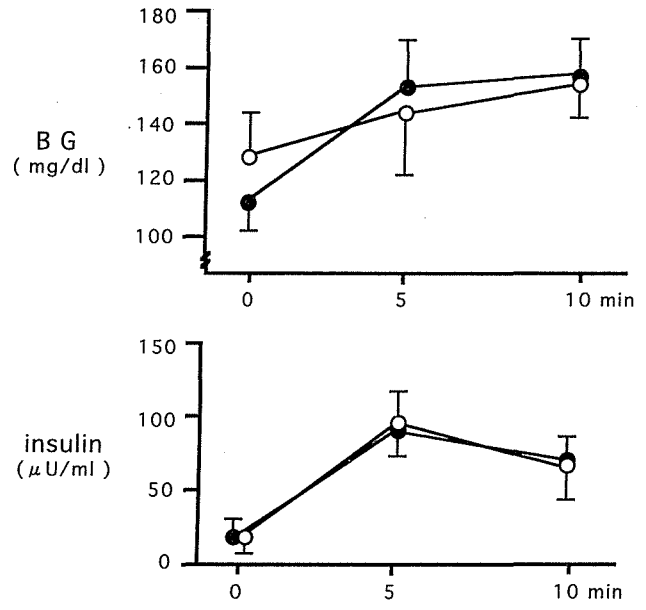


Fig. 2 Blood glucose and plasma insulin responses to arginine
 ○ portal stimulation, ● peripheral stimulation
 The values are means \pm SD.

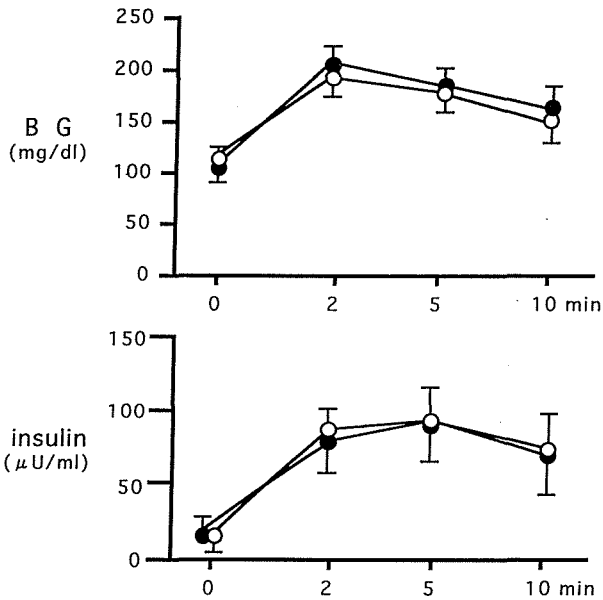


Fig. 3 Blood glucose and plasma insulin responses to glucose after atropine treatment
 ○ portal stimulation, ● peripheral stimulation
 The values are means \pm SD.

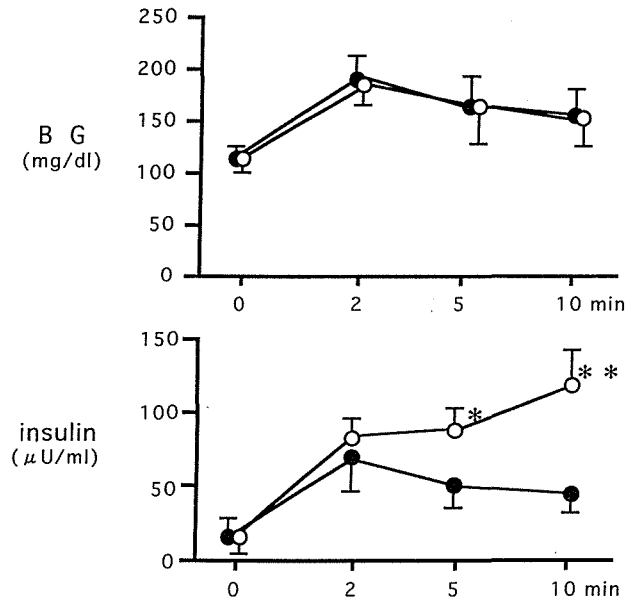


Fig. 4 Blood glucose and plasma insulin responses to glucose after propranolol treatment
 ○ portal stimulation, ● peripheral stimulation
 The values are means \pm SD.
 *p < 0.05 and **p < 0.01 vs. peripheral stimulation.

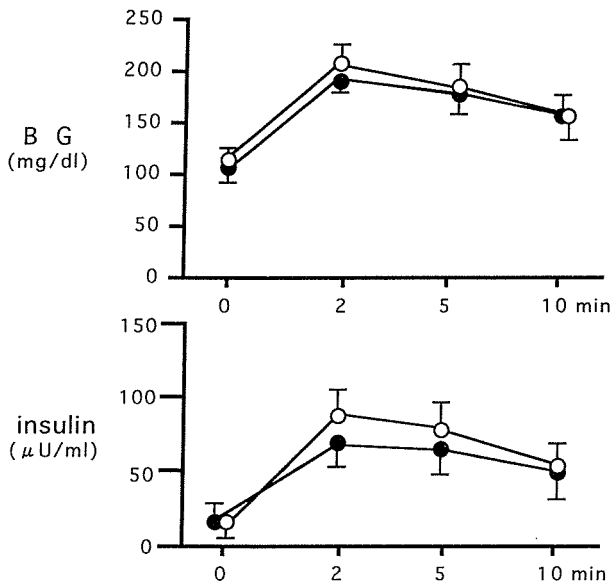


Fig. 5 Blood glucose and plasma insulin responses to glucose after atenolol treatment
 ○ portal stimulation, ● peripheral stimulation
 The values are means ± SD.

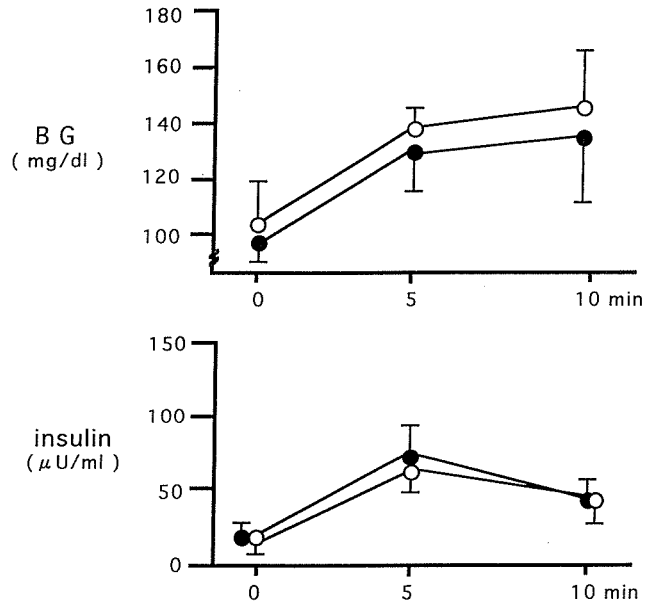


Fig. 6 Blood glucose and plasma insulin responses to arginine after atropine treatment
 ○ portal stimulation, ● peripheral stimulation
 The values are means ± SD.

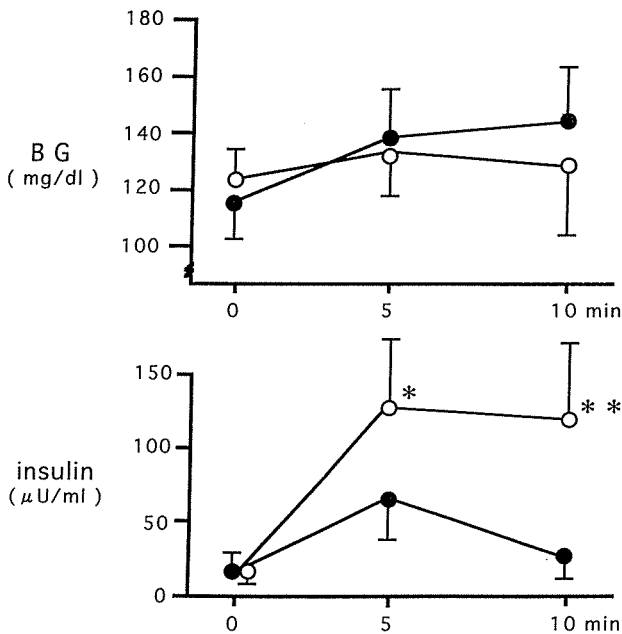


Fig. 7 Blood glucose and plasma insulin responses to arginine after propranolol treatment
 ○ portal stimulation, ● peripheral stimulation
 The values are means ± SD.
 * $p < 0.05$ and ** $p < 0.01$ vs. peripheral stimulation.

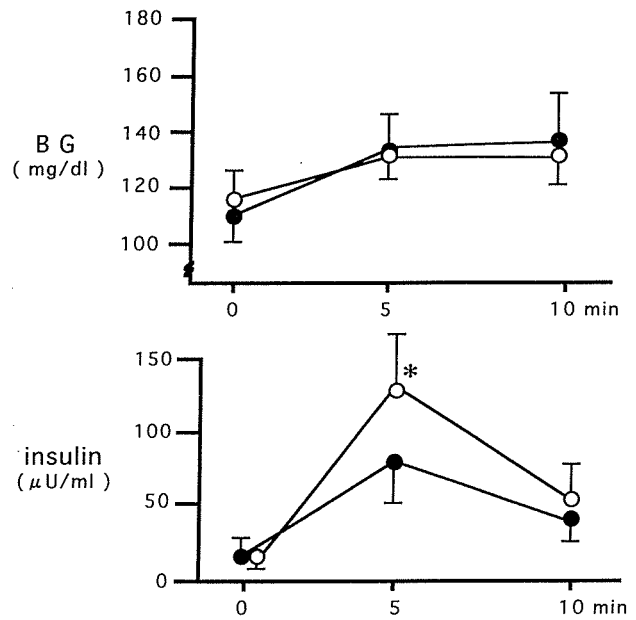


Fig. 8 Blood glucose and plasma insulin responses to arginine after atenolol treatment
 ○ portal stimulation, ● peripheral stimulation
 The values are means ± SD.
 * $p < 0.05$ vs. peripheral stimulation.

DISCUSSION

In the present study, insulin concentration secreted after portal administration of glucose or arginine was not significantly different from that after peripheral administration of glucose or arginine, and atropine pretreatment did not significantly change the insulin response to portal glucose or arginine. These results suggest that cholinergic mechanisms have no important role in insulin secretion in response to portal glucose or arginine. The present results were contradictory to the results of previous studies. Lee and Miller⁹⁾ and Okazaki et al.¹⁰⁾ found that hepatic vagotomy decreases insulin response (in the arterial blood or jugular vein) to intraperitoneal glucose administration. Tanaka et al.^{4,6)} suggested that the hepatic branch of the vagus nerve contains arginine-sensitive afferent fibers which sense portal arginine concentrations and send signals to the brainstem centers, which then inhibit the activities of the vagal efferent pancreatic neuroendocrine system after intraperitoneal arginine stimulation. The reason for the discrepancy in the results is unclear. Glucose or arginine was infused directly into the portal vein, and portal insulin concentration was measured to avoid the influence of hepatic insulin extraction in the present study. This may explain the difference in the results.

It is generally accepted that β -adrenergic antagonist decreases insulin secretion induced by a variety of stimuli^{11,12)}. In the present study, the glucose-induced insulin secretion to portal stimulation was significantly enhanced by the preadministration of propranolol, and arginine-induced insulin secretion to portal stimulation was also significantly enhanced by the preadministration of propranolol or atenolol. There have been only a few reports regarding the role of the adrenergic system in hepato-portal glucose-or arginine-receptors. Tanaka et al.⁶⁾ suggested that sympathetic pathways are not involved in the arginine sensor-mediated pancreatic neuroendocrine system. However, the present results suggest that the β -adrenergic mechanisms have some role in insulin response to portal stimulation of glucose or arginine. Namely, hepato-portal receptors for glucose inhibit insulin secretion via β 2-adrenergic mechanisms and receptors for arginine also inhibit insulin secretion via β 1- and β 2-adrenergic mechanisms. In the study of Tanaka et al., arginine was administered intraperitoneally in the rat three days after surgery⁶⁾. The difference in the results may be due to the difference of the experimental methods. Although portal stimulation of glucose or arginine significantly increased insulin releases after propranolol administration, blood glucose level did not decrease in the present study. Blood glucose level may decrease 10 minutes after.

What role might glucose and arginine receptors play in the physiological state? It is well known that insulin secreted after an oral glucose administration is influenced by gastro-intestinal factors, and a number of studies have delineated the role of gastro-intestinal hormones, often termed the enteroinsular axis, in the modulation of insulin secretion¹³⁻¹⁵⁾. Thus, several gastro-intestinal hormones secreted after an oral nutrient can enhance insulin secretion. Therefore, glucose and arginine receptors in the hepato-portal system may act to inhibit their glucose-or arginine-induced exaggerated insulin secretion after glucose or protein from the gastrointestinal tract.

In summary, we conclude that there are receptors for glucose and arginine in the hepato-portal system, and that glucose and arginine receptors may inhibit insulin secretion via β -adrenergic mechanisms.

SUMMARY

To elucidate the possible role of the hepato-portal system in glucose-or arginine-induced insulin secretion, insulin response to intraportal (portal stimulation) or intravenous (peripheral stimulation) glucose or arginine infusion was investigated in the rat. The glucose-or arginine-induced insulin secretion was not significantly different between portal stimulation and peripheral stimulation. The glucose-or arginine-induced insulin secretion was significantly higher in portal stimulation than in peripheral stimulation after propranolol pretreatment (0.5mg/kg, sc). The glucose-induced insulin release was not significantly changed by atenolol pretreatment. However, the arginine-induced insulin release was significantly higher in portal stimulation than in peripheral stimulation after atenolol pretreatment (50mg/kg, sc).

These results suggest that there are receptors for glucose and arginine in the hepato-portal system, and that the hepato-portal receptors for glucose and arginine inhibit insulin secretion via β -adrenergic mechanisms.

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