Effect of Cephalic Glucose Infusion on Insulin Secretion

R. A. Chieri,* J. M. S. Farina, J. Halperin and J. C. Basabe*

Institute of Physiology, Buenos Aires Medical School, Argentina

Sumary. The continous infusion of glucose (1 mg/kg/min) via the carotid artery in anesthetized dogs produces a biphasic pattern of insulin secretion. The first peak reaches a maximum 3 min after glucose infusion and drops to basal level at 7 min. As long as the glucose infusion persists a slow and mantained increase in insulin level in the pancreaticoduodenal vein can be observed. The same amount of glucose infused in the general circulation via the jugular vein provoked a different pattern of insulin secretion. Cerebral glucose infusion to vagotomized dogs also produced a two phase response in insulin secretion, but the levels reached in the first phase were lower that those observed in the normal dogs. The infusion of glucose, via the jugular vein, in vagotomized dogs, failed to induce any change in plasma insulin levels. Our data suggest that a glucose load to the brain induces pancreatic insulin secretion mediated partially by the vagus nerves. These results are also compatible with the hypothesis that a humoral factor could be involved in the pancreatic response.

Key-words: Insulin secretion; vagus nerves; cephalic glucose infusion.

The role of the nervous system in the control of blood sugar level was recognized many years ago [2]. Sympathetic and adrenal function were implicated in the neural mechanism of hyperglycemia [4]. The physiological role played by the vagus nerves on the control of blood sugar level has been a conflicting issue. Although early workers reported enhanced insulin secretion associated with vagal stimulation [5, 8], the fact that the transplanted pancreas was able to maintain blood sugar homeostasis, diminished the importance of vagal control of insulin secretion [9, 13]. Stimulation of the vagus nerve has been reported to produce no changes [17] or increase in plasma immunoreactive insulin [6, 8, 14, 18].

The hypothalamus is also involved in the maintenance of blood sugar homeostatis.Rats with electrolytic lesions of the ventromedial region have improved glucose tolerance tests and increased sensitivity to insulin [21]. The improvement of the diabetic glucose tolerance of the sand rat after hypothalamic injury has also been described [3]. Furthermore, androgenized female rats developed diabetes sooner than the normal animals when subjected to partial pancreatectomy [7]. In guinea pigs, electrolytic lesions of the anterior and middle hypothalamus were followed by insulin hypersensitivity and lower fasting blood sugar levels [1]. Evidence for an insulin-sensitive receptor in the central nervous system [19] and for a central adrenergic regulation of insulin has also been reported [20].

The present experiment was designed to help resolve the unsettled question concerning the role played by the central nervous system on the control of insulin secretion.

Material and Methods

Normal and vagotomized mongrel dogs of either sex, weighing between 17 to 20 kg were used. Bilateral vagotomy was accomplished at the intra-thoracic portion of the nerve at the level of the lower third of the esophagus. A period of ten days elapsed between surgery and the experimental procedure, to avoid the influence of stress.

Experimental Procedure

After eighteen hours of fasting the normal or vagotomized dogs were anesthetized by intravenous injection of nembutal (33 mg/kg) and submitted to the following surgical procedure: the pyloric region was approached through a medial laparatomy, a polyethylene cathether was placed in the pancreaticoduodenal vein via the right gastroepiploic vein. Both carotid arteries were canulated with a polyethylene tube through the lower thyroid artery. A fourth polyethylene tube was placed in a branch of the femoral artery.

After surgery the animals were allowed to rest for one hour to stabilize the basal condition. They were kept under nembutal anesthesia during the experimental period.

  * Members of Carrera del Investigador Científico, Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina.

At 0 time, blood samples were withdrawn from the pancreatico-duodenal vein and the femoral artery. Glucose or saline infusion was then started immediately, via the carotid artery or the jugular vein (depending on the group studied) at a dose of 1 mg/min/kg and continously maintained during one hour using a Harvard infusion pump. Blood samples from the pancreatico-duodenal vein and the femoral artery were taken at different times for insulin and glucose determination. Blood sugar was determined by the Somogyi Nelson method [16]. Plasma immunoreactive insulin was determined by the Herbert method [10].

The following groups were studied: 1. Normal dogs infused with glucose (0.34 mM) via carotid artery. 2. Normal dogs infused with sodium chloride (0.34 mM) via carotid artery. 3. Normal dogs infused with sodium chloride (0.17 mM) via carotid artery. 4. Normal dogs infused with glucose (0.34 mM) via jugular vein. 5. Normal dogs infused with sodium chloride (0.34 mM) via jugular vein. 6. Vagotomized dogs infused with glucose (0.34 mM) via carotid artery. 7. Vagotomized dogs infused with glucose (0.34 mM) via jugular vein.

Statistical analysis was performed by the t test. The values observed in each group during the infusion period was compared with its basal values.

Results

1. Effect of Glucose Infusion into the Carotid Artery on Insulin Secretion

The infusion of glucose into the carotid artery produced an increase in the insulin levels in the pancreatico-duodenal vein with a two-phase pattern of secretion. The first peak reached a maximum 3 min after glucose infusion and at 7 min dropped to near basal level. As long as glucose infusion persisted, a slow and maintained increase in insulin levels in the pancreatico-duodenal vein was observed. The insulin output reached a maximum at 40 min. From 60 to 90 minutes, the time after the glucose infusion was stopped, plasma insulin dropped to basal levels. Plasma insulin values in the general circulation began to increase from 7 min until the end of the experiment; no two-phase pattern was observed and the values were lower than those observed in the pancretico-duodenal vein. Blood sugar levels remained unchanged throughout the entire experiment (Table 1).

The same amount of glucose infused in the general circulation via the jugular vein provoked a different pattern of insulin secretion. A slow but steady increase in plasma insulin was detected in the pancreatico-

duodenal vein from 15 to 60 min; from 60 to 90 min plasma insulin levels dropped to basal values.

Plasma insulin and blood sugar levels determined in the general circulation (femoral artery) showed no change, remaining at basal values during the entire experiment (Table 1).

The infusion of isotonic (0.17 mM) or hypertonic (0.34 mM) sodium chloride solution into the carotid artery did not provoke any pancreatic response. Similarly, the infusion of isotonic sodium chloride solution in the general circulation did not modify the glycemia and insulinaemia (Table 2).

2. Effect of Vagotomy on the Response to Cerebral Glucose Infusion

Cerebral glucose infusion to vagotomized dogs changed the pancreatic response previously described in normal dogs. A two-phase response was also observed in insulin secretion but the levels reached in the first phase were statistically lower than the observed in the normals ($p < 0.05$ at 3 and 5 min). In the second phase, although the values obtained were not statistically different a tendency to a diminished insulin secretion was observed. No changes in plasma insulin levels were detected in blood from the femoral artery, probably as a consequence of the diminished insulin output. The blood sugar level remains unchanged throughout the experiment (Table 1).

The infusion of glucose via the jugular vein in vagotomized dogs failed to provoke any changes in plasma insulin levels and glycemia (Table 1).

As a summary of the results obtained, in Fig. 1 the values of plasma insulin levels determined in the pancreatico-duodenal vein for the different groups studied are shown.

Discussion

The present experiment demonstrates that glucose infusion to the brain, via the carotid artery, elicits a pancreatic response shortly after the beginning of infusion, which lasted as long as infusion was maintained. This effect was not caused by alterations in the circulating volume or in the osmolarity of blood reaching the central nervous system, since isotonic or hypertonic sodium chloride infusion failed to provoke any changes in the plasma immunoreactive insulin levels. Likewise, the modifications observed were not a consequence of the glucose acting at other levels of the body, since jugular infusion of glucose at the same dose was unable to provoke the same pancreatic response. Vagotomy diminished the pancreatic insulin release triggered by the infusion of glucose to the

Table 1

Time min	Glucose infusion carotid artery						Glucose infusion jugular vein					
	Normal dogs			Vagotomized dogs			Normal dogs			Vagotomized dogs		
	Insulin (IRI) panc. duod. vein μU/ml X±S.E.M.	Insulin (IRI) femoral artery μU/ml X±S.E.M.	Glycemia femoral artery mg/100 ml X±S.E.M.	Insulin (IRI) panc. duod. vein μU/ml X±S.E.M.	Insulin (IRI) femoral artery μU/ml X±S.E.M.	Glycemia femoral artery mg/100 ml X±S.E.M.	Insulin (IRI) panc. duod. vein μU/ml X±S.E.M.	Insulin (IRI) femoral artery μU/ml X±S.E.M.	Glycemia femoral artery mg/100 ml X±S.E.M.	Insulin (IRI) panc. duod. vein μU/ml X±S.E.M.	Insulin (IRI) femoral artery μU/ml X±S.E.M.	Glycemia femoral artery mg/100 ml X±S.E.M.
0	68.6±12.8 (8)	23.9±3.1 (8)	97.0±7.0 (7)	68.2±13.9 (4)	27.1±5.1 (4)	89.7± 8.2 (4)	49.1±12.7 (4)	19.0± 8.3 (4)	90.0± 7.9 (4)	91.0± 8.4 (3)	21.8±7.7 (3)	86.3± 9.3 (3)
1	107.6±18.9 (8)	19.9±3.2 (8)	92.5±8.2 (6)	75.2±11.0 (4)	23.0±2.6 (4)	88.2± 9.6 (4)	63.7± 9.1 (4)	19.9± 7.9 (4)	91.7± 4.6 (4)	91.7± 4.4 (3)	23.3±7.2 (3)	88.7±11.7 (3)
3	222.0±26.5 (8)[b]	27.5±5.1 (8)	93.1±4.5 (7)	113.6±10.3 (4)[a]	25.7±3.2 (4)	86.7±10.3 (4)	80.7±17.9 (4)	17.8± 6.8 (4)	97.2± 5.1 (4)	82.5± 9.5 (3)	25.3±8.7 (3)	92.7±10.3 (3)
5	202.2±22.3 (8)[b]	28.0±4.3 (8)	88.4±5.6 (7)	114.7± 6.2 (4)	20.6±4.9 (4)	86.5±12.2 (4)	92.2±24.8 (4)	19.4± 7.0 (4)	98.2± 5.4 (4)	89.8±12.2 (3)	16.8±8.4 (3)	93.0±11.8 (3)
7	102.0±48.6 (5)	34.7±5.1 (6)[a]	98.8±6.4 (7)	98.2± 4.4 (4)	22.7±3.9 (4)	89.0±13.7 (4)	89.7±12.3 (4)	16.5± 6.1 (4)	101.0± 5.1 (4)	101.0±11.2 (3)	23.8±5.7 (3)	92.3± 6.6 (3)
10	157.6±26.1 (8)[b]	32.1±4.8 (8)	95.7±7.2 (7)	116.5± 1.9 (4)[a]	22.2±3.4 (4)	89.7±14.1 (4)	82.5±15.3 (4)	22.5± 7.8 (4)	96.5± 6.8 (4)	92.0±11.7 (3)	21.5±7.3 (3)	86.7± 9.3 (3)
15	221.5±35.5 (8)[c]	35.5±3.9 (8)	95.3±7.8 (7)	131.7±10.4 (4)[a]	22.1±5.7 (4)	92.2±12.8 (4)	104.5± 3.3 (4)[c]	23.3± 6.8 (4)	97.7±11.5 (4)	103.7± 8.7 (3)	14.7±5.2 (3)	83.3±11.1 (3)
20	233.0±44.8 (8)[c]	39.2±6.7 (8)[a]	93.3±4.7 (7)	178.0±13.2 (4)[c]	27.7±4.6 (4)	94.5±11.4 (4)	107.5± 6.6 (4)[b]	20.0± 5.1 (4)	97.0± 7.2 (4)	109.7± 7.4 (3)	18.0±4.0 (3)	88.3± 4.6 (3)
30	267.9±48.4 (7)[c]	37.9±4.6 (8)[a]	100.4±6.7 (7)	198.5±21.4 (4)[c]	37.7±5.1 (4)	94.5±11.4 (4)	101.0± 5.6 (4)[b]	26.9± 8.0 (4)	100.7± 9.8 (4)	106.7± 4.4 (3)	20.7±6.1 (3)	88.3± 4.6 (3)
40	317.9±55.5 (8)[c]	40.7±5.6 (8)[a]	97.0±8.2 (7)	198.9±21.5 (4)[c]	27.1±9.2 (4)	95.5±12.3 (4)	110.7± 7.4 (4)[b]	21.3± 4.7 (4)	92.2± 2.9 (4)	108.8±10.9 (3)	23.5±7.1 (3)	89.7± 5.8 (3)
50	287.9±38.1 (7)[d]	55.9±8.9 (8)[a]	95.6±7.9 (7)	214.0±33.7 (4)	28.1±7.6 (4)	89.5±12.0 (4)	112.5±11.8 (4)[a]	22.1± 3.7 (4)	87.5± 7.6 (4)	96.5± 9.2 (3)	15.3±2.7 (3)	86.7±12.9 (3)
60	278.6±36.2 (8)[d]	54.3±8.2 (8)[b]	93.7±8.5 (7)	222.0±32.6 (4)[b]	28.2±6.1 (4)	88.2±10.8 (4)	120.0± 7.3 (4)[c]	23.4±10.0 (4)	84.5± 8.7 (4)	94.7± 9.2 (3)	23.0±5.7 (3)	93.0±10.0 (3)
70	161.7±29.8 (8)[d]	48.1±9.9 (8)[a]	93.3±7.8 (7)	168.0±37.5 (4)[a]	26.2±9.3 (4)	89.0±14.5 (3)	76.7±16.7 (4)	21.4± 6.9 (4)	86.0±10.5 (4)	103.0± 4.0 (3)	28.5±8.4 (3)	89.0± 6.3 (3)
80	138.9±43.3 (8)[a]	52.2±9.7 (8)[a]	95.3±8.6 (7)	155.2±29.0 (4)[a]	29.1±4.1 (4)	94.7±11.7 (4)	50.0±11.4 (4)	17.1± 3.6 (4)	82.2± 3.4 (4)	108.3± 7.7 (3)	22.8±9.5 (3)	93.7± 9.5 (3)
90	115.7±28.3 (8)	42.4±9.6 (8)[a]	93.6±9.3 (6)	103.1±16.9 (4)	29.5±4.5 (4)	95.5±12.1 (4)	56.2±12.8 (4)	22.0± 6.9 (4)	86.5± 8.4 (4)	98.0± 9.1 (3)	21.8±6.5 (3)	86.7± 9.2 (3)

a $p < 0.05$ c $p < 0.005$
b $p < 0.01$ d $p < 0.001$

Glucose and insulin levels in normal and vagotomized dogs after glucose infusion (1 mg/kg/min) via carotid artery or jugular vein. Levels of significance were calculated for the difference between basal and infusion concentrations of IRI.

Table 2

Time min	Sodium chloride infusion carotid artery (0.17M)			Sodium chloride infusion carotid artery (0.34M)			Sodium chloride infusion jugular vein (0.34M)		
	Insulin (IRI) panc. duod. vein μU/ml X±S.E.M.	Insulin (IRI) femoral artery μU/ml X±S.E.M.	Glycemia femoral artery mg/100 ml X±S.E.M.	Insulin (IRI) panc. duod. vein μU/ml X±S.E.M.	Insulin (IRI) femoral artery μU/ml X±S.E.M.	Glycemia femoral artery mg/100 ml X±S.E.M.	Insulin (IRI) panc. duod. vein μU/ml X±S.E.M.	Insulin (IRI) femoral artery μU/ml X±S.E.M.	Glycemia femoral artery mg/100 ml X±S.E.M.
0	76.7±21.4 (4)	20.0±6.3 (4)	115.0±15.6 (3)	78.7±7.2 (3)	23.3±10.4 (3)	104.0±5.7 (3)	118.5±14.7 (4)	52.5±8.6 (4)	98.8±8.9 (4)
1	74.4±19.8 (4)	18.0±5.2 (4)	114.7±8.0 (3)	70.0±15.0 (3)	24.8±9.9 (3)	106.0±5.0 (3)	108.2±14.1 (4)	57.2±10.5 (4)	95.0±8.9 (4)
3	62.7±20.3 (4)	17.7±7.4 (4)	108.7±10.7 (3)	75.7±16.9 (3)	17.7±6.5 (3)	108.0±4.3 (3)	104.4±18.2 (4)	48.5±12.4 (4)	95.0±10.8 (4)
5	64.0±14.3 (4)	16.6±6.2 (4)	118.3±17.0 (3)	77.3±14.5 (3)	15.0±7.6 (3)	98.0±10.8 (3)	106.6±17.2 (4)	51.9±14.2 (4)	95.7±6.7 (4)
7	77.2±5.0 (4)	22.9±3.9 (4)	117.3±14.5 (3)	59.2±24.8 (3)	20.0±2.9 (3)	91.7±13.0 (3)	112.0±11.2 (4)	43.2±9.4 (4)	97.5±5.2 (4)
10	75.1±25.4 (4)	17.5±5.4 (4)	118.3±13.0 (3)	77.0±22.5 (3)	16.7±7.3 (3)	94.3±3.8 (3)	111.2±11.8 (4)	47.6±13.4 (4)	96.7±6.6 (4)
15	69.7±19.7 (4)	17.0±5.2 (4)	119.0±16.1 (3)	78.3±16.1 (3)	21.7±4.9 (3)	100.3±0.3 (3)	112.2±13.2 (4)	48.6±11.7 (4)	98.2±8.4 (4)
20	71.2±17.4 (4)	17.2±5.7 (4)	114.0±9.4 (3)	74.8±13.9 (3)	17.8±5.1 (3)	102.7±6.5 (3)	105.1±17.7 (4)	46.1±4.7 (4)	88.7±9.6 (4)
30	70.0±15.3 (4)	20.5±6.0 (4)	107.3±8.1 (3)	86.0±20.1 (3)	26.0±5.0 (3)	101.3±2.4 (3)	114.1±7.3 (4)	50.1±10.9 (4)	93.7±7.5 (4)
40	76.2±20.6 (4)	17.7±4.8 (4)	106.7±8.3 (3)	68.3±18.2 (3)	18.3±10.8 (3)	96.7±9.1 (3)	116.5±9.5 (4)	43.2±15.0 (4)	91.2±8.3 (4)
50	72.2±23.5 (4)	16.1±6.9 (4)	110.0±7.8 (3)	72.3±20.8 (3)	21.0±10.2 (3)	99.7±5.5 (3)	111.7±8.9 (4)	41.8±11.3 (4)	91.2±6.2 (4)
60	71.5±22.7 (4)	22.0±7.9 (4)	108.7±13.3 (3)	81.7±25.5 (3)	17.0±7.2 (3)	98.7±4.7 (3)	107.0±6.2 (4)	46.6±6.5 (4)	92.5±5.0 (4)
70	76.5±16.9 (4)	18.6±3.6 (4)	110.7±16.0 (3)	80.7±20.8 (3)	20.2±3.9 (3)	92.3±10.8 (3)	117.0±7.9 (4)	45.5±6.5 (4)	92.2±7.3 (4)
80	74.0±22.7 (4)	16.5±2.9 (4)	106.7±18.3 (3)	75.8±18.8 (3)	26.8±8.4 (3)	102.0±7.0 (3)	124.7±16.4 (4)	62.5±6.6 (3)	94.5±6.4 (4)
90	76.5±24.2 (4)	16.7±4.9 (4)	107.7±19.7 (3)	70.2±23.1 (3)	21.7±6.0 (3)	104.3±6.3 (3)	127.8±18.1 (3)	63.7±9.1 (3)	90.7±6.2 (4)

Glucose and insulin levels in normal dogs after sodium chloride (0.17 or 0.34 mM) via carotid artery or jugular vein.

brain, but did not eliminate it. This would suggest that other mechanisms, besides the vagus nerve, are probably involved in the observed response.
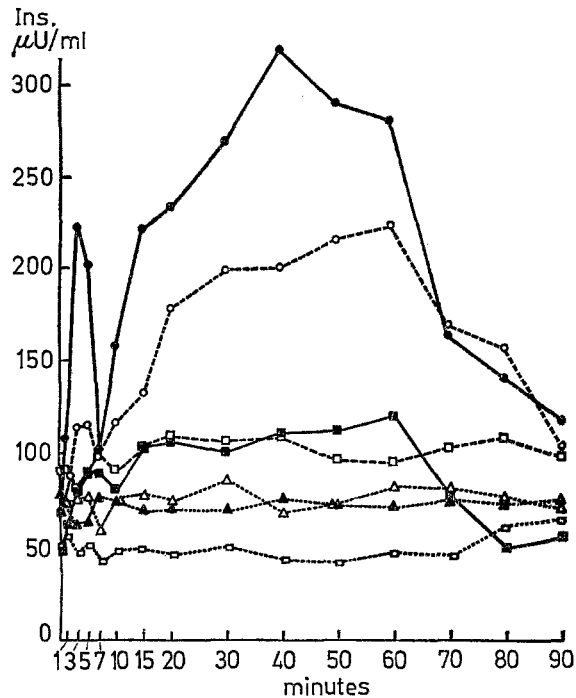

Fig. 1. Insulin levels in the pancreaticoduodenal vein after glucose or sodium chloride infusion via the carotid artery or the jugular vein

Glucose and Sodium Chloride Infusion Carotid Artery
●—●—● Glucose in normal dogs
O--O--O Glucose in vagotomized dogs
△⋯△⋯△ Na Cl 0.34 mM in normal Dogs
▲⋯▲⋯▲ Na Cl 0.17 mM in normal dogs
Glucose and Sodium Chloride Infusion Jugular Vein
■—■—■ Glucose in normal dogs
□--□--□ Glucose in vagotomized dogs
□⋯□⋯□ Na Cl 0.34 mM in normal dogs

Previous reports demonstrate that the ventrolateral hypothalamus secretes a humoral factor which provokes insulin secretion [11, 12, 15]. It has also been shown that local infusion of glucose to the ventro medial hypothalamus, provokes on augmentation in the rate of discharge of some neurones, suggesting the existence of glucose sensitive neurones [18]. It could be speculated that the arrival of glucose at the brain could provoke insulin secretion by at least two different mechanisms; one mechanism involving the vagus nerves, as has been demonstrated in the present investigation and the second one could be the secretion of a humoral factor. The existence of this humoral response to the arrival of glucose would explain why vagotomy was not capable of eliminating the insulin response to the central infusion of glucose.

The results obtained with the infusion of glucose via the jugular vein, in normal and vagotomized dogs deserve a separate comment. In the normal dogs, although insulin secretion did not reach the levels observed when glucose was infused via the carotid artery, it showed a mild but maintained increase in insulin output from 15 min after the infusion was started until the end of infusion, when it dropped to basal levels. On the contrary, the infusion of glucose via jugular vein in vagotomized dogs did not elicit any pancreatic response, clearly demonstrating that systemic infusion of glucose, at the dose employed acts as a stimulus for insulin secretion only when the vagus nerves are intact.

A possible explanation for this phenomenon is that vagotomy could provoke trophic alterations of the B-cells, causing a diminution in their sensitivity to glucose. Another hypothesis is that the response observed in the normal dogs, to the systemic glucose load, was mainly a vagal reflex, suggesting that the central nervous receptors for glucose have a lower glucose threshold than the B-cells. The fact that jugular infusion of glucose to normal dogs, at the dose employed, provoked insulin secretion without changes in systemic blood sugar level, deserves comment. This behavior can be explained assuming that the cephalic glucoreceptors are very sensitive and detect smaller changes in blood sugar levels than our method for blood sugar determination.

Further studies are being carried out in our laboratory to clarify the physiological role played by the neuroendocrine mechanism for insulin secretion suggested by this investigation.

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Dr. R. A. Chieri
Institute of Physiology
Buenos Airos Medical School
Buenos Aires
Argentinia