Studies on the Mechanism of Xylitol-induced Insulin Secretion in Dogs

Effect of its Infusion into the Pancreatic Artery, and the Inhibition by Epinephrine and Diazoxide of Xylitol-induced Hyperinsulinaemia

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Summary. The effect of infusion of small doses of xylitol into the pancreatic artery upon insulin release was studied in anaesthetized dogs, in order to decide whether the strong insulin-releasing effect of xylitol in dogs is mediated by a direct action of xylitol upon the islets or indirectly by some of its metabolites. Xylitol or glucose was infused at 0.5 — 1.0 mg/kg · min either into the femoral vein or into the superior pancreaticoduodenal artery, and the changes in plasma insulin were measured in the superior pancreaticoduodenal vein. Infusion into the pancreatic artery always resulted in a sharp increase in insulin release, whereas intravenous infusion caused no or little increase. Infusion of xylitol into the superior pancreaticoduodenal artery produced a prompt increase in plasma insulin in the superior pancreaticoduodenal vein but not in the splenic vein. These data suggest that xylitol has a direct stimulatory effect upon islet cells. — During intravenous infusion of epinephrine (1.0 µg/kg. min), plasma insulin did not increase despite intravenous administration of glucose or xylitol (0.4 g/kg). There was a rebound rise of plasma insulin after cessation of epinephrine infusion. Plasma insulin responses to intravenous injection of glucose or xylitol (0.4 g/kg) were inhibited also by the intravenous infusion of diazoxide (0.2 mg/kg · min), but this was somewhat variable among individual dogs. The suppression by epinephrine or diazoxide of both glucose- and xylitol-induced hyperinsulinaemia may suggest that there is some common mechanism between the insulin-releasing effects of glucose and xylitol.

Etudes sur le mécanisme de la sécrétion d'insuline provoquée par le xylitol chez des chiens. Effet de son infusion dans l'artère pancréatique, et inhibition par l'adrénaline et le diazoxide de l'hyperinsulinémie provoquée par le xylitol

Résumé. L'effet sur la sécrétion d'insuline de l'infusion de petites doses de xylitol dans l'artère pancréatique a été étudié chez des chiens anesthésiés, afin de savoir si l'effet fortement insulino-sécréteur du xylitol chez les chiens est dû à une action directe du xylitol sur les îlots ou à une action indirecte par l'intermédiaire de certains de ses métabolites. Le xylitol ou le glucose était infusé à la dose de 0.5 — 1.0 mg/kg. min, soit dans la veine fémorale, soit dans l'artère pancréatico-duodénale supérieure, et les variations de l'insuline plasmatique étaient mesurées dans la veine pancréatico-duodénale supérieure. L'infusion dans l'artère pancréatique provoquait toujours une rapide augmentation de la sécrétion d'insuline, tandis que l'infusion intraveineuse ne causait pas ou peu d'augmentation. L'infusion de xylitol dans l'artère pancréatico-duodénale supérieure provoquait une augmentation prompte de l'insuline plasmatique dans la veine pancréatico-duodénale supérieure, mais pas dans la veine splénique. Ces données suggèrent que le xylitol a un effet stimulateur direct sur les cellules des îlots. — Pendant l'infusion intraveineuse d'adrénaline (1.0 µg/kg. min), l'insuline plasmatique n'augmentait pas malgré l'administration intraveineuse de glucose ou de xylitol (0.4 g/kg). Après l'arrêt de l'infusion d'adrénaline, l'insuline plasmatique présentait un phénomène de rebound. Les réponses de l'insuline plasmatique à l'injection intraveineuse de glucose ou de xylitol (0.4 g/kg) étaient également inhibées par l'infusion intraveineuse de diazoxide (0.2 mg/kg. min), mais ceci était un peu variable selon les chiens. La suppression par l'adrénaline ou le diazoxide de l'hyperinsulinémie provoquée par le glucose et le xylitol peut suggérer qu'il existe un mécanisme commun entre les effets insulino-sécréteurs du glucose et du xylitol.

Untersuchungen zum Mechanismus der verstärkten Insulinsekretion unter Xylit. Effekte seiner Infusion in die Pankreasarterie und Hemmung der Xylit-bedingten Hyperinsulinaemie durch Adrenalin und Diazoxid

Zusammenfassung. An anaesthesierten Hunden wurde die Wirkung der Infusion kleiner Xylit-Mengen in die Pankreasarterie auf die Insulinfreisetzung untersucht, um zu klären, ob das Xylit direkt oder über einen seiner Metabolite auf die Insulinausschüttung wirkt. Xylit oder Glucose wurde in Mengen von 0.5 — 1.0 mg/kg/min entweder in die Femoralvene oder in die A.pankreatico-duodenalis sup. infundiert und die Änderung des Plasma-Insulins in der V.pankreatico-duodenalis sup. gemessen. Zufuhr über die Pankreasarterie löste immer eine abrupte Steigerung der Insulinfreisetzung aus, während intravenöse Gaben zu keinem oder nur einem geringen Anstieg führten. Die Xylit-Infusion in die A.pankreatico-duodenalis sup.bewirkte zwar eine prompte Steigerung der Plasma-Insulinspiegel in der V.pankreatico duodenalis sup., nicht aber in der Milzvene. — Diese Befunde sprechen dafür, daß Xylit die Inselzellen direkt stimuliert. Während einer i.v.Infusion von 1.0 µg/kg/min Adrenalin stieg das Plasma-Insulin trotz intravenöser Zufuhr von 0.4 g/kg Glucose oder Xylit nicht an. Nach Beendigung der Adrenalin-Infusion wurde ein verstärkter Wiederanstieg des Plasma-Insulins beobachtet. Auch durch i.v.-Gaben von 0.2 mg/kg/min Diazoxid ließ sich die Wirkung der Infusion von 0.4 g/kg Glucose oder Xylit unterdrükken, wobei sich jedoch Unterschiede zwischen den einzelnen Tieren ergaben. Die Aufhebung des Xylit- u. Glucose-Effektes auf die Insulinsekretion durch Adrenalin und Diazoxid könnte darauf hinweisen, daß die Steigerung der Insulinfreisetzung durch Glucose und Xylit auf einem gemeinsamen Mechanismus beruht.

Key-words: Insulin secretion, local vs. systemic infusions, glucose, xylitol, epinephrine, diazoxide.

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Introduction

Striking xylitol-induced hyperinsulinaemia in dogs was first reported by Hirata et al. [5] and by us [8]. Our previous study disclosed that this effect of xylitol in dogs becomes more pronounced with higher doses, and that xylitol is more effective than glucose, even when administered orally [9]. It is likely that the hyperinsulinaemia results from augmented secretion of insulin from the pancreas, because plasma insulin concentration in the pancreatic vein promptly increased after intravenous injection of xylitol, paralleling that in the peripheral vein [9]. It was suggested that some metabolic processes or intermediates which are common to both glucose and xylitol may be directly related to the mechanism of insulin secretion.

However, it is not yet certain whether xylitol itself acts directly upon the islets or whether insulin secretion is stimulated by a metabolite. Consequently, we have investigated the effect of infusion into the pancreatic artery of a small dose of xylitol previously shown to be ineffective when used systemically. Furthermore, the inhibitory effects of epinephrine [12] and diazoxide [4] upon xylitol-induced insulin secretion were also studied.

Methods

Animals.

Adult dogs of mixed breed of 7—15 kg were fed a controlled diet for at least one week, and subjected to the experiment after an overnight fast.

Infusions of glucose and xylitol into the superior pancreaticoduodenal artery. Dogs were anaesthetized with intravenous sodium pentobarbital (25—30 mg/kg), and laparotomized in supine position. The superior pancreaticoduodenal vessels were severed from the surrounding tissue, and the branching points of the right gastroepiploic vessels were exposed. A Teflon catheter (2 mm in diameter) was inserted into the right gastroepiploic vein, and its tip placed just beyond the junction of this vessel with the superior pancreaticoduodenal vein (Fig. 1). Then a Teflon catheter (1 mm in diameter) was inserted into the right gastroepiploic artery and threaded upstream to reach the superior pancreaticoduodenal artery. The main duodenal branches of the superior pancreaticoduodenal vessels were ligated to minimize the extrapancreatic distribution of the infused substance and the dilution of secreted insulin by the blood coming from the duodenum. These procedures usually took about one hour. Collection of the first blood sample was begun 60—90 min after the end of these procedures. Blood samples were withdrawn from the femoral artery by an indwelling needle and from the pancreaticoduodenal vein by the catheter described above. Both the arterial needle and the pancreatic vein catheter were filled with heparinized saline (10 U/ml) after each blood sampling. Heparinized saline was constantly infused at a rate of 25—50 ml/h through the pancreatic artery catheter to keep it patent. Glucose or xylitol was in-

fused either through this catheter or into the femoral vein for 15—30 min in a dose of 0.5—1 mg/kg. min, with a constant rate of 50 ml/h with the help of an infusion pump. Successive infusions were given after intervals of at least 60 min.

In one experiment, splenectomy was performed and an additional catheter was inserted into the splenic vein. The tip of this catheter was placed about 1 cm
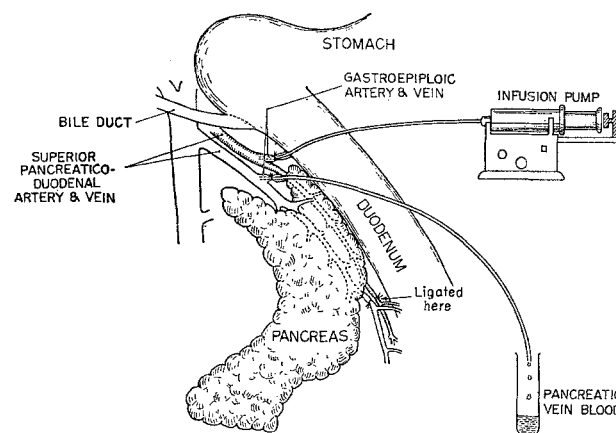

Fig. 1. Diagram of catheterizations into the superior pancreaticoduodenal artery and vein. The catheters were inserted through the right gastroepiploic vessels
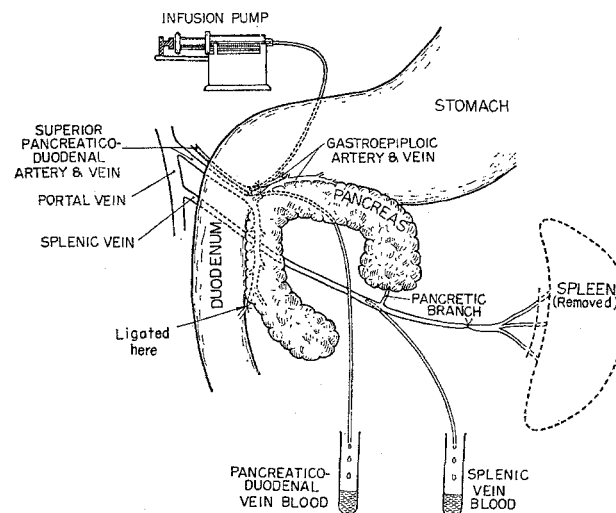

Fig. 2. Diagram of blood sampling from the superior pancreaticoduodenal vein and the splenic vein. In addition to catheterizations into the superior pancreaticoduodenal artery and vein, a catheter was inserted into the splenic vein after splenectomy

downstream from the site where the last pancreatic branch was flowing in. Glucose and xylitol, 0.5 mg/kg· min, were infused into the superior pancreaticoduodenal artery, and blood was withdrawn simultaneously from the femoral artery, superior pancreaticoduodenal vein and splenic vein (Fig. 2).

Effect of infusion of epinephrine and diazoxide upon xylitol- or glucose-induced hyperinsulinaemia. Dogs were anaesthetized with sodium pentobarbital and kept su-

pine. About 90 min after anaesthesia, three control blood samples were withdrawn from the femoral vein at 15 min intervals. Constant infusion of epinephrine (1 µg/kg. min) into the femoral vein at 25—50 ml/ 60 min was then started and continued for 60 min. Glucose or xylitol, 0.4 g/kg, was injected as 20% solution into the femoral vein over 10 min from the 20th to the 30th min of epinephrine infusion. Blood samplings were carried out repeatedly during, and for 120 min after, the infusion of epinephrine. To prevent oxidation of epinephrine, it was diluted with saline containing 2 mg/ml ascorbic acid.

The diazoxide experiments were performed in the same way as the epinephrine experiments. Diazoxide (100—150 mg) was dissolved in 100 ml saline by gradual addition of NaOH and warming. The final pH was 10.5—11.0. This solution was infused into the femoral vein at 0.2 mg/kg. min for 60 min. Glucose or xylitol, 0.4 g/kg, was administered intravenously from the 20th to the 30th min after diazoxide infusion was started.

Treatment of blood samples. Blood samples were centrifuged within one hour. Plasma was kept frozen at — 20°C. Plasma glucose was determined by a glucose-oxidase method. Xylitol was measured by a periodate oxidation method [1] after deproteinization according to SOMOGYI [14]. Plasma insulin was assayed by a double antibody radioimmunoassay using dog insulin standard [7].

Results

1. Infusions of small doses of glucose or xylitol into the femoral vein and into the pancreatic artery. In 2 dogs, glucose was infused at 1.0 mg/kg · min first into the femoral vein for 15 min, then after an interval of one hour into the pancreaticoduodenal artery for 15 min. In 2 other dogs, these two infusions were given in the reverse order (Table 1). The intravenous infusion of this small amount of glucose did not increase significantly in each case plasma glucose and insulin in the femoral artery and in the pancreatic vein. By contrast, infusion of glucose into the pancreaticoduodenal artery produced prompt increases of both glucose and insulin levels in the pancreatic vein, and also of insulin levels in the femoral artery. However, arterial glucose did not increase significantly. After cessation of infusion, plasma glucose in the pancreatic vein decreased promptly, returning to the control level within 15 min, and insulin returned to the pre-infusion level within 30 min. Five dogs received infusions of xylitol (1.0 mg/ kg · min) into the femoral vein and into the pancreaticoduodenal artery, each for 15 min, with an interval of one hour in between. Infusions were given first into the femoral vein and then into the pancreaticoduodenal artery in 3 dogs, and the order was reversed in 2 dogs (Table 2). Plasma glucose showed no significant change. Plasma xylitol and insulin levels in the femoral artery and pancreatic vein did not rise significantly after intravenous infusion of xylitol. During infusion into the pancreaticoduodenal artery, plasma xylitol in the pancreatic vein and plasma insulin in the femoral

artery and pancreatic vein clearly increased, but the xylitol levels in the femoral artery did not increase. There were marked individual variations in the magnitude of the increases in glucose and xylitol concentrations in the pancreatic vein during infusion into the pancreaticoduodenal artery of these substances.
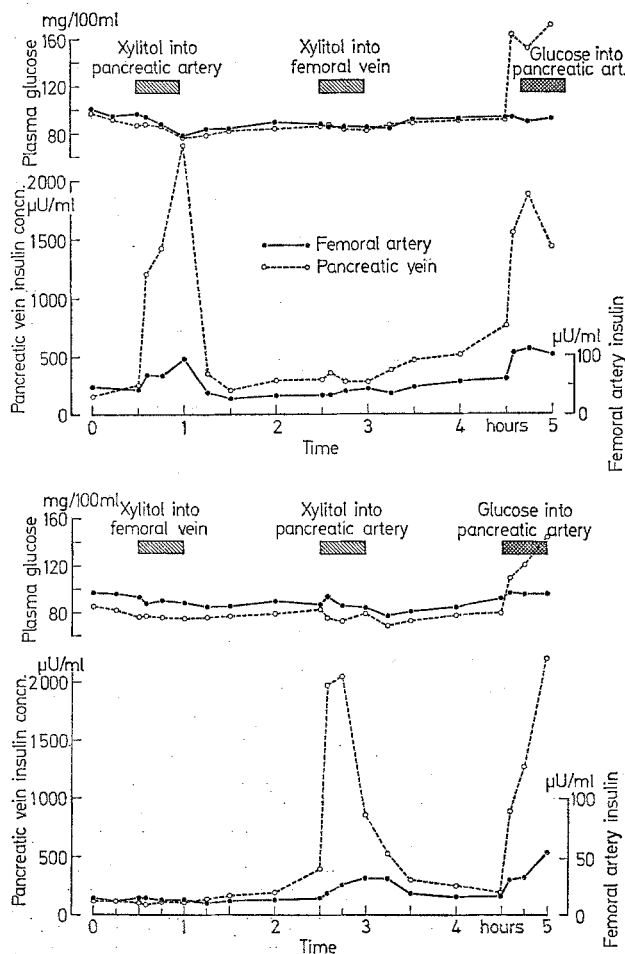

Fig. 3. Effect of the infusions of xylitol into the pancreatic artery and femoral vein and of glucose into the pancreatic artery upon plasma glucose and insulin concentrations in 2 dogs. Xylitol and glucose were infused at 0.5 mg/kg·min for 30 min. Plasma insulin increased in the pancreatic vein and in the femoral artery when these substances were infused into the pancreatic artery, but remained unchanged by the systemic intravenous infusion of xylitol

Two experiments were carried out similarly, but with slower and more protracted (0.5 mg/kg.min over 30 min) infusion. The results were similar (Fig. 3). Plasma insulin in the pancreatic vein and in the femoral artery did not change as a result of intravenous infusions of glucose or xylitol, but increased clearly when these substances were administered into the superior pancreaticoduodenal artery.

The results of an experiment in which blood was taken both from the superior pancreaticoduodenal vein and the splenic vein are presented in Fig. 4. During

glucose or xylitol infusion into the superior pancreatico-duodenal artery, plasma glucose or xylitol concentration increased markedly in the superior pancreatico-duodenal vein, but did not rise in the femoral artery and in the splenic vein. Plasma insulin in the superior pancreaticoduodenal vein increased sharply during the infusions, but the insulin levels in the splenic vein did not show a clear increase.

Xylitol (0.4 g/kg) was administered intravenously during the infusion of epinephrine in the same animals that received the infusion of epinephrine alone (Fig. 7). This dose usually produces a prompt and marked rise in plasma insulin [5, 8]. During epinephrine infusion, however, administration of xylitol did not cause any increase in plasma insulin. Plasma xylitol level and its disappearance curve were not significantly different
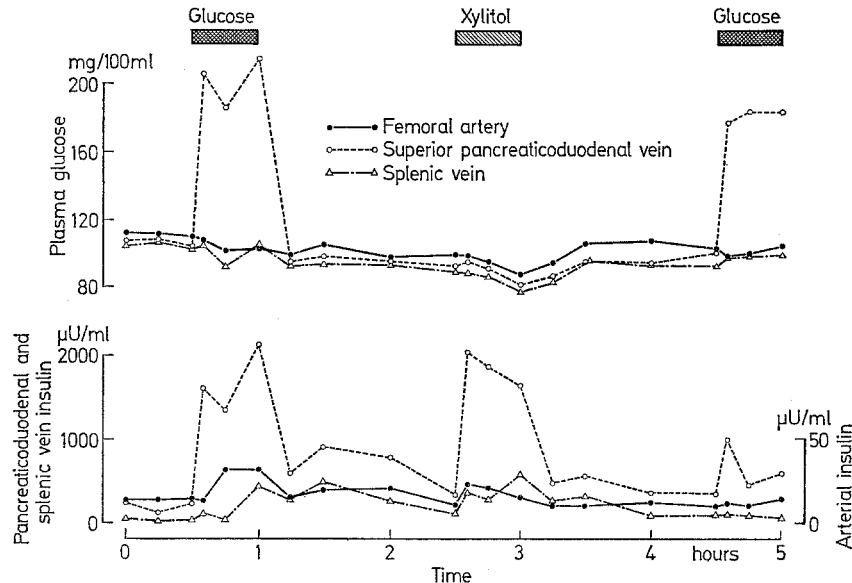

Fig. 4. Changes in plasma glucose and insulin in the femoral artery, superior pancreaticoduodenal vein and splenic vein during the infusions of glucose and xylitol into the superior pancreaticoduodenal artery. Plasma insulin in the superior pancreaticoduodenal vein increased promptly but plasma insulin in the splenic vein did not rise clearly

2. Effect of epinephrine infusion on glucose- or xylitol-induced hyperinsulinaemia

When epinephrine was infused at a rate of 1 µg/kg. min, plasma glucose increased promptly and remained high throughout the infusion (Fig. 5). It tended to decrease 5—10 min after the end of the infusion, but the mean plasma glucose level was still higher than the preinfusion level, 2 hours after cessation of the infusion. During the infusion, plasma insulin did not increase at all despite marked hyperglycaemia, but following the cessation of infusion it rose promptly.

When glucose (0.4 g/kg) was given intravenously during epinephrine infusion, plasma glucose reached 450—528 mg/100 ml, then gradually decreased (Fig. 6). Plasma insulin did not increase significantly during the infusion of epinephrine, but rose immediately after the end of infusion[1].

whether xylitol was given alone[1] or during epinephrine infusion. Immediately after termination of epinephrine infusion, there was again a rebound rise of plasma insulin. When xylitol was administered, the elevated plasma glucose either decreased slightly or remained unchanged, despite no increase in plasma insulin. Plasma glucose remained elevated for about 30 min after the end of epinephrine infusion, then tended to decrease.

3. Effect of diazoxide infusion on glucose- or xylitol-induced hyperinsulinaemia

In most cases, plasma glucose increased slightly after the infusion of diazoxide was started. The degree of hyperglycaemia produced during diazoxide infusion was variable among individual dogs. Following administration of glucose, plasma glucose reached the peak of 280—369 mg/100 ml immediately, and decreased thereafter, but the glucose tolerance curve was much retarded (Fig. 8). Plasma insulin tended to decrease during diazoxide infusion, and remained low despite glucose loading in 4 dogs, but in one dog there was a prompt rise of plasma insulin after glucose injection. It is interesting that fairly good glucose to-

[1] Our control values for plasma insulin (mean of 5 dogs) at 0, 10, 20, 30, and 60 min after intravenous administration of glucose (0.4 g/kg) were 65, 68, 51, 35, and 22 µU/ml respectively. Plasma insulin and xylitol levels (mean of 5 dogs) at 0, 10, 20, 30, and 60 min after intravenous administration of xylitol (0.4 g/kg) were 111, 188, 167, 118 and 43 µU/ml for insulin [8] and 160, 81, 43, 18 and 9 mg/100 ml for xylitol respectively.

Table 1. *Effects of the infusions of glucose (1 mg/kg·min) into the superior pancreaticoduodenal artery and into the femoral vein upon plasma glucose and insulin concentrations in the femoral artery and the superior pancreaticoduodenal vein*

Dogs		Time (minutes)																				
		0	15	30	32	35	40	45	50	60	75	90	105	107	110	115	120	125	135	150	165	180
					First infusion[a]										Second infusion[a]							
8.3 kg ♂	AG	93	91	82	89	82	88	78	77	75	83	90	86	87	92	89	89	94	91	90	89	85
	PVG	85	85	76	125	121	118	128	77	65	72	79	79	83	85	81	79	80	88	79	83	77
	AI	21	20	17	22	22	28	25	21	17	12	13	16	16	18	17	18	24	19	14	12	10
	PVI	360	380	300	1750	750	970	870	640	280	290	270	230	700	360	390	370	260	600	340	200	310
10.2 kg ♂	AG	112	102	113	114	115	112	110	106	94	102	106	102	100	106	102	97	102	90	97	85	99
	PVG	94	81	92	214	240	276	236	114	94	94	93	86	91	91	96	93	92	85	90	92	92
	AI	16	13	18	26	35	28	32	32	18	8	18	12	6	11	12	10	11	4	8	4	8
	PVI	260	340	370	2210	1640	1760	2090	3140	3080	500	540	260	220	250	230	250	160	150	210	140	150
13.1 kg ♂	AG	65	67	60	62	63	68	64	63	61	59	59	66	65	63	71	67	66	49	42	59	57
	PVG	61	60	51	59	55	67	60	54	55	54	48	55	125	138	146	177	66	42	39	47	52
	AI	9	6	6	8	8	7	9	7	7	7	8	8	160	187	172	179	141	40	12	9	8
	PVI	45	55	50	70	60	50	55	55	45	45	50	60	17600	11900	10100	10150	3420	180	60	50	30
14.4 kg ♂	AG	111	105	104	108	105	105	108	99	92	91	91	92	103	104	99	92	87	82	101	105	104
	PVG	83	82	81	81	81	86	84	77	69	74	73	82	327	368	365	373	116	73	83	88	84
	AI	29	28	28	32	29	32	29	22	23	23	17	19	89	83	62	64	49	17	21	26	28
	PVI	870	1420	1720	1380	1340	1780	1270	1030	940	690	890	780	16900	9700	8300	9700	5930	1620	1730	2130	1920

[a] The infusions were started just after taking 30 min or 150 min samples and terminated immediately after taking 45 min or 120 min samples.

P = into the pancreatic artery
AG = femoral artery glucose (mg/100 ml)
AI = femoral artery insulin (μU/ml)

F = into the femoral vein
PVG = pancreatic vein glucose (mg/100 ml)
PVI = pancreatic vein insulin (μU/ml)

Table 2. *Effects of the infusions of xylitol (1 mg/kg·min) into the superior pancreaticoduodenal artery and into the femoral vein upon plasma glucose, xylitol and insulin concentration in the femoral artery and the superior pancreaticoduodenal vein*

		0	15	30	32	35	40	45	50	60	75	90	105	107	110	115	120	125	135	150	165	180
					First infusion[a]										Second infusion[a]							
10.0 kg ♂	AG	98	92	101	98	105	100	96	93	95	98	105	99	97	100	99	101	102	105	109	113	123
	PVX	6	—	0	62	76	70	86	18	2	1	—	2	2	2	6	4	3	3	0	—	0
	AI	29	18	26	30	54	61	64	50	41	28	20	20	26	25	25	27	22	23	31	33	40
	PVI	160	150	200	1660	1520	1200	610	810	100	90	240	170	110	230	190	160	120	290	260	250	670
11.4 kg ♂	AG	126	117	130	120	130	129	121	112	104	104	118	121	122	119	122	119	118	135	124	135	130
	PVX	0	—	2	128	141	162	171	18	4	2	—	3	3	3	4	5	0	1	0	—	0
	AI	33	22	32	26	49	65	63	65	44	28	22	25	24	36	30	26	23	47	36	45	36
	PVI	160	260	380	1520	2200	2370	1050	900	650	580	290	380	370	470	530	500	260	940	1020	1700	890
13.0 kg ♀	AG	95	98	97	97	100	95	91	85	87	92	90	92	92	90	88	84	78	71	75	89	92
	PVX	0	—	3	3	4	4	5	4	3	0	—	1	195	193	214	213	31	8	8	—	7
	AI	13	13	14	15	19	13	14	10	9	9	6	8	36	38	41	44	40	25	13	14	15
	PVI	175	150	135	150	190	140	160	105	130	180	185	200	2400	1130	1750	1380	1700	560	220	310	300
13.8 kg ♂	AG	83	90	95	92	92	88	91	92	93	97	100	100	101	101	92	93	95	99	92	95	98
	PVX	0	—	0	2	3	3	4	2	0	1	—	0	133	150	171	168	10	2	1	—	0
	AI	16	—	20	25	31	40	30	13	12	15	29	14	26	26	37	76	30	24	18	21	16
	PVI	180	90	110	140	130	150	100	110	130	120	180	110	380	390	270	320	260	180	130	100	140
14.2 kg ♂	AG	96	96	98	92	94	98	85	94	86	102	95	92	102	103	102	89	92	102	100	105	111
	PVX	0	—	0	1	2	2	3	2	0	0	—	0	46	32	33	29	0	0	0	—	0
	AI	36	—	23	38	40	23	19	19	19	12	15	18	27	28	32	36	36	18	10	12	9
	PVI	150	440	100	290	240	100	240	100	240	190	240	320	940	540	460	470	170	120	150	120	190

[a] The infusions were started just after sampling at 30 min or 150 min and terminated immediately after sampling at 45 min or 120 min.

P = into the pancreatic artery
AG = femoral artery glucose (mg/100 ml)
AI = femoral artery insulin (μU/ml)

F = into the femoral vein
PVX = pancreatic vein xylitol (mg/100 ml)
PVI = pancreatic vein insulin (μU/ml)

Data of pancreatic vein glucose and arterial xylitol are omitted because of the absence of any significant changes.

lerance was preserved in this dog. There was a tendency for a gradual increase of plasma insulin after termination of diazoxide infusion.

Plasma glucose continued to increase following xy-

litol administration (Fig. 9). Despite the impaired glucose tolerance during diazoxide infusion, the changes in plasma xylitol were not significantly different from control experiments in which xylitol was given alone.
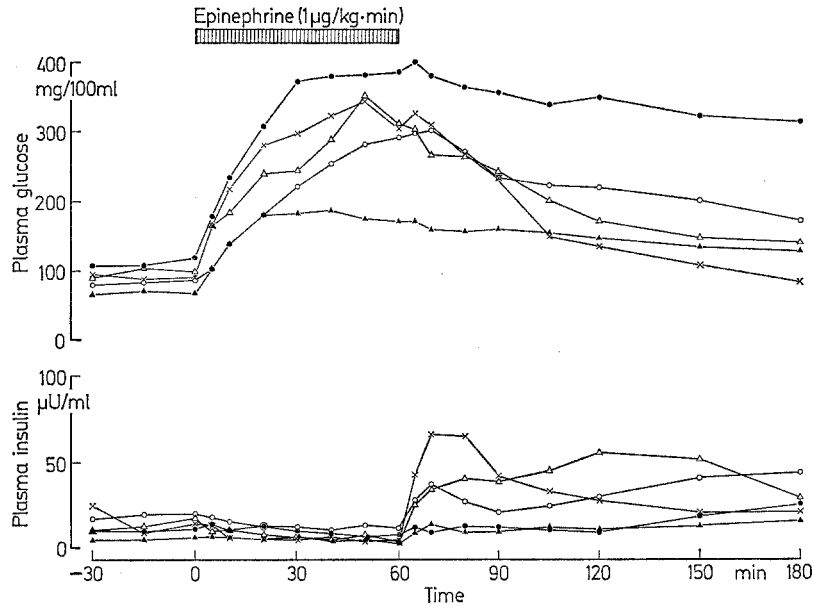

Fig. 5. Effect of infusion of epinephrine upon plasma glucose and insulin in 5 anaesthetized dogs. Epinephrine was infused intravenously at a rate of 1.0 µg/kg·min for 60 min. Different symbols denote different dogs. Plasma insulin did not increase despite hyperglycaemia during epinephrine infusion. It rose promptly after the termination of infusion
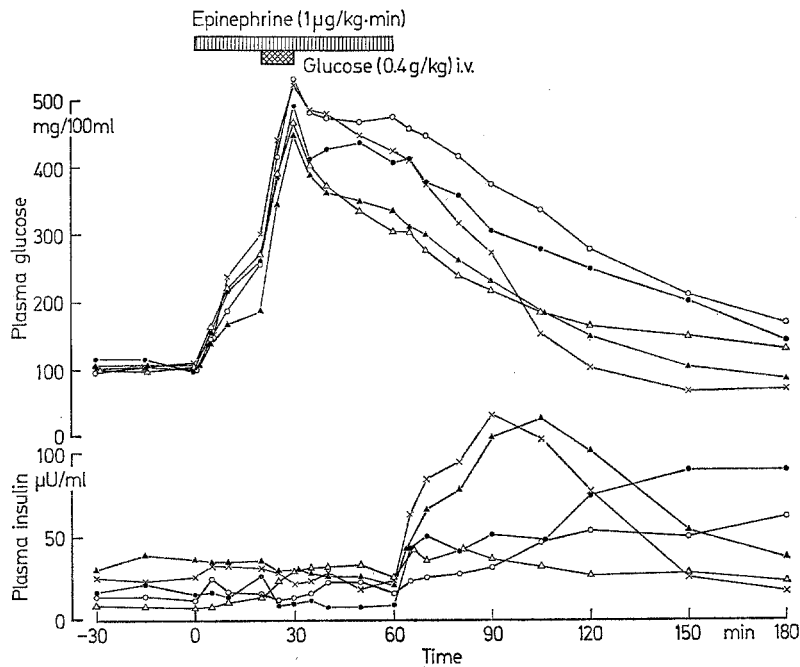
Fig. 6. Inhibition of glucose-induced insulin secretion by the infusion of epinephrine. Epinephrine was infused at 1.0 µg/kg·min for 60 min. Glucose (0.4 g/kg) was given intravenously over 10 min during epinephrine infusion. Plasma insulin did not increase significantly during the infusion of epinephrine, but rose promptly after the end of infusion. Different symbols denote different animals
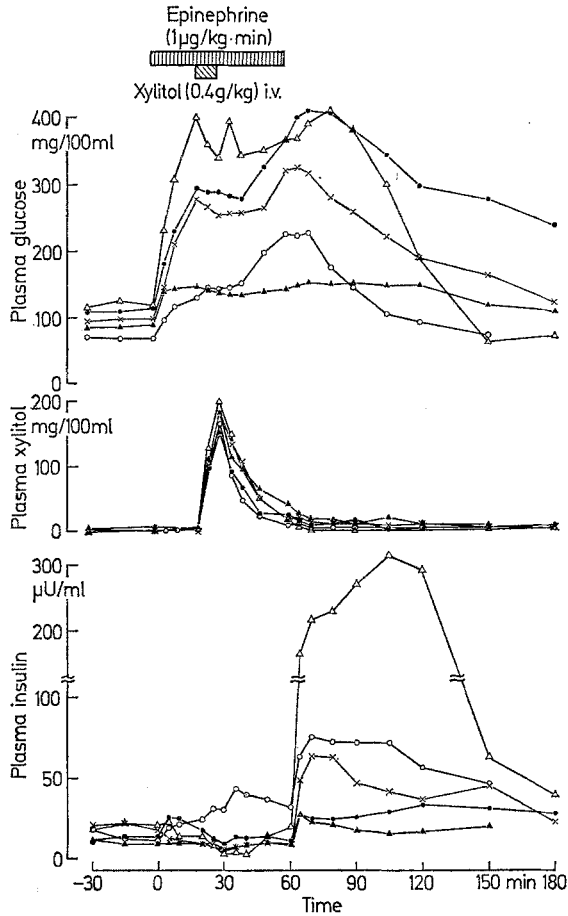
Fig. 7. Inhibition of xylitol-induced insulin secretion by the infusion of epinephrine. Epinephrine was infused intravenously at 1.0 µg/kg · min for 60 min. Xylitol (0.4 g/kg) was injected intravenously over 10 min during epinephrine infusion. Plasma insulin did not rise during the infusion of epinephrine. It increased promptly after the cessation of infusion. Different symbols denote different animals
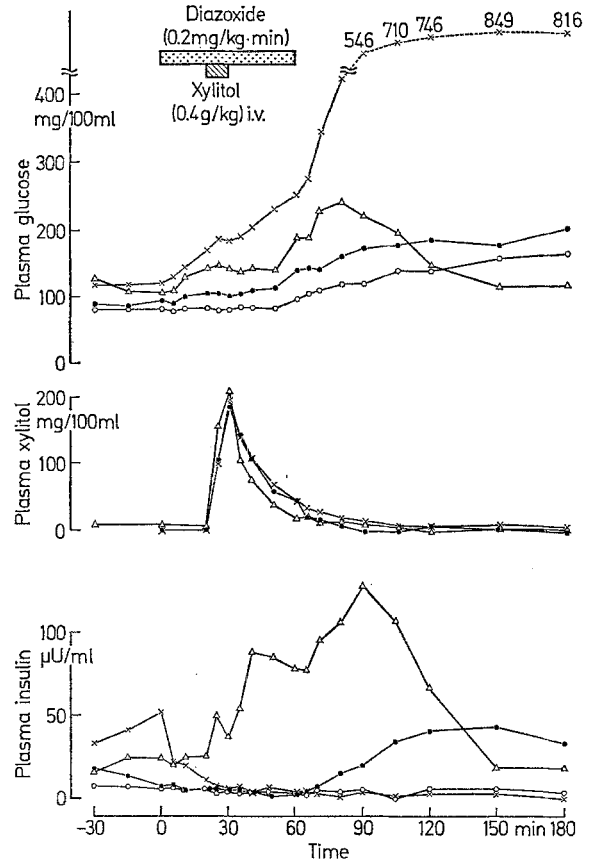
Fig. 9. Effect of the infusion of diazoxide upon xylitol-induced insulin secretion. Diazoxide was infused at a rate of 0.2 mg/kg · min for 60 min. Xylitol (0.4 g/kg) was given intravenously over 10 min during the infusion of diazoxide. In 3 out of 4 dogs, plasma insulin response to xylitol was completely suppressed by diazoxide infusion. Different symbols denote different dogs
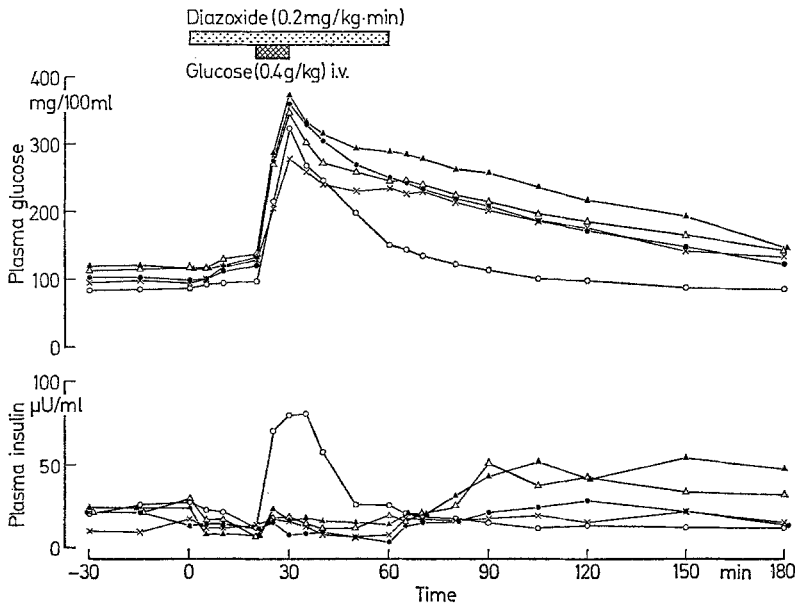

Fig. 8. Effect of the infusion of diazoxide upon glucose-induced insulin secretion. Diazoxide was infused at a rate of 0.2 mg/kg · min for 60 min. Glucose (0.4 g/kg) was given intravenously during the infusion of diazoxide. Different symbols denote different animals. In 4 out of 5 dogs, the rise of plasma insulin following glucose loading appears to be suppressed by diazoxide infusion

Plasma insulin did not rise at all in 3 dogs after xylitol injection, but it increased clearly in one dog. Plasma insulin tended to rise slightly following cessation of diazoxide infusion.

Discussion

Our previous studies [8, 9] showed that systemic administration of xylitol, particularly at high doses, caused a marked increase in plasma insulin in dogs, exceeding the hyperinsulinaemia resulting from equivalent doses of glucose. However, it was still uncertain whether this strong effect of xylitol resulted from its direct action upon the islets, or whether it was converted to a metabolite which in turn stimulated the secretion of insulin. In our present study, infusion of small doses of glucose or xylitol, which were almost totally ineffective by the systemic intravenous route, produced a marked increase in plasma insulin in the pancreatic vein when administered into the superior pancreaticoduodenal artery. When xylitol or glucose was infused into the superior pancreaticoduodenal artery and blood samples were taken both from the superior pancreaticoduodenal vein and the splenic vein, the clear increase in plasma insulin was observed only in the former vein, which drained the portion of the pancreas perfused by the superior pancreaticoduodenal artery. All these data support the direct local action of xylitol upon islets, although they do not necessarily mean that xylitol stimulates the beta cells directly, since it is still possible that alpha cells or other pancreatic cells, which are also exposed to a high concentration of xylitol during infusion, might release glucagon or another insulinotropic substance, thereby stimulating insulin secretion indirectly. However, the rapidity of the insulin-releasing response to xylitol infusion seems to favour the view that its main effect is the result of a direct action upon beta cells. This is in accord with the observation of MONTAGUE et al. [11], who reported that xylitol stimulated the release of insulin from isolated rat islets. Our data do not rule out the possiblity that some metabolite of xylitol may also be effective in stimulating insulin secretion. Although our impression is that the effect of xylitol did not exceed that of glucose when administered in the pancreatic artery, quantiative comparison of the insulinotropic effect of xylitol with that of glucose is very difficult in our local infusion experiments, because of the marked variations in the plasma levels of xylitol or glucose and of insulin in the pancreatic vein during the infusions. This variation is probably attributable mainly to the individual variation of the vascular system of the dog pancreas, which is perfused by several different arteries, and also to unavoidable, small changes in the position of the catheter tip. Variation in the relative contribution and blood flow of each vessel may lead to variable dilution of the infused substance.

Epinephrine and diazoxide are known to suppress the secretion of insulin both *in vivo* [12, 4] and *in*

vitro [11, 3]. In our experiments, inhibition of insulin release by epinephrine was observed in all cases, but the inhibitory effect of diazoxide was more variable for both glucose- and xylitol-mediated insulin response. Although the reason for this variability is unknown, it is possible that the effect of diazoxide is mediated not only by a direct action on the islet, but also by some indirect one mediated by adrenergic hormones [6]; thus the mechanism of its inhibition of insulin release *in vivo* may be more complex than that of epinephrine.

Among various insulin-releasing substances, the effect of arginine is not suppressed either by epinephrine or by diazoxide [2, 13], and the inhibitory effect of diazoxide upon insulin secretion is reported to be counteracted by tolbutamide [3, 10]. In this respect, the insulinotropic effect of xylitol appears similar to that of glucose rather than to that of arginine or sulphonylureas. The present data may suggest the possibility that the insulin-releasing actions of glucose and xylitol share some common mechanism.

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