Plasma Insulin Concentrations in Dogs and Monkeys After Xylitol, Glucose or Tolbutamide Infusion

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SUMMARY

Beagle dogs and Rhesus monkeys were infused with xylitol, glucose, or tolbutamide at intervals of ten to fourteen days. Infusion of all three agents produced significant increases in mean plasma insulin concentrations in both species. In dogs, xylitol produced the highest insulin concentrations followed by glucose and tolbutamide in that order, while in monkeys, glucose produced the highest insulin concentrations followed by tolbutamide and xylitol. The insulinotropic effect of both xylitol and glucose in the monkey was abolished by simultaneous infusion of epinephrine. Results suggest that glucose and xylitol stimulate release of insulin through a common metabolite of the pentose phosphate pathway. However, unexplained quantitative differences exist between the monkey and dog with respect to the insulinotropic response to these agents. DIABETES *19*:17-22, 1970.

In the dog, xylitol is a more potent insulinotropic agent than glucose.[1,3] In man, the evidence for this is inconclusive, however. Kuzuya et al.[4] found that xylitol increased plasma insulin concentrations, but its stimulatory effect was less than that of glucose, while Geser et al.[5] did not demonstrate any insulinotropic effect of xylitol in man. Accordingly, to obtain further information on the effects of xylitol we have compared the plasma insulin response after infusion of xylitol, glucose or tolbutamide in both dogs and a nonhuman primate. Distinctly different response patterns were obtained in the two species.

MATERIAL AND METHODS

Rhesus monkeys (*Macaca mulatta*), one male and three females, weighing 4.1 to 6.1 kg. were individually caged and fed Purina monkey chow for one year prior to the investigation. Their ages were estimated between six and eight years. Purebred beagle dogs, five males and five females, weighing 8.3 to 11.3 kg., were individually caged and fed Masters dog chow for at least three months prior to the investigation. Their ages varied from twelve to eighteen months.

Animals, fasted overnight, were anaesthetized by intravenous injection of 25 to 30 mg./kg. of sodium pentobarbital. Cannulae were inserted into the left and right saphenous veins. Thirty minutes after the induction of anesthesia, a heparinized control blood sample was taken from one cannula, and a second sample was taken fifteen minutes later. The volumes of the blood samples were 2 ml. each for monkeys and 4 ml. each for dogs.

Two monkeys and two dogs were infused with 2 ml./kg. of 0.15 M NaCl solution to determine the effects of handling and anesthesia alone on plasma insulin and glucose concentrations. Xylitol and glucose were each infused at a dose of 2 ml. of a 20 per cent solution/kg. (0.4 gm./kg.). Sodium tolbutamide was infused at a dose of 2 ml. of a 2.5 per cent solution/kg. (50 mg./kg.). Each animal received the three treatments in a random sequence, with ten to fourteen days elapsing between experiments. Each dog received each of the three tests once, while each monkey received each of the three tests twice.

Immediately after collecting the second control sample (zero time), one half of the test dose was infused over a two-minute period, via the opposite cannula, and a third blood sample was taken three minutes after the end of the infusion (at five minutes). The other half of the test dose was infused between five and seven minutes, and a fourth blood sample was taken three minutes after the end of the infusion (at ten minutes). Two additional blood samples were withdrawn at thirty and sixty minutes making a total of six samples from each animal in each experiment. Plasma was separated by centrifugation and stored at —20° C. until the com-

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TABLE 1

Plasma insulin concentrations in dogs (ng./ml.)

No.	Sex	Substance infused*	Minutes —15	0	5	10	30	60
817	M	X	0.1	0.1	1.4	3.4	3.0	0.3
		G	ND+	0.1	0.9	1.4	1.9	0.6
		T	0.1	0.1	0.5	0.6	2.4	0.6
996	M	X	0.8	0.9	1.1	10.5	4.5	2.5
		G	0.6	0.6	5.9	5.2	3.1	3.5
		T	0.3	0.5	1.3	1.6	0.8	0.3
247	M	X	0.2	0.3	1.5	5.3	4.8	1.5
		G	ND	ND	1.0	2.3	2.8	0.4
		T	0.4	0.4	0.8	1.6	2.5	1.9
972	M	X	0.4	0.1	0.2	3.6	3.0	0.8
		G	1.5	1.0	1.3	3.8	2.5	1.1
		T	1.0	1.0	1.5	1.8	4.9	2.9
338	M	X	0.3	0.3	0.9	3.9	3.4	0.4
		G	0.3	0.7	1.0	2.5	1.1	0.3
		T	0.3	0.3	1.1	0.8	0.9	1.1
898	F	X	0.5	0.6	3.1	5.6	4.8	3.0
		G	0.8	0.1	2.5	4.8	0.8	1.1
		T	0.8	0.1	5.6	5.0	5.7	2.8
210	F	X	0.5	0.3	3.0	8.4	7.5	1.5
		G	0.4	0.2	3.5	4.5	4.5	1.8
		T	0.7	0.7	2.8	2.2	1.8	1.0
335	F	X	0.6	0.3	2.9	4.5	4.3	2.0
		G	0.8	0.9	1.8	2.6	2.3	1.5
		T	1.0	0.9	1.8	1.9	0.9	1.1
337	F	X	ND	0.1	2.5	3.5	2.1	1.3
		G	0.5	0.2	1.8	1.5	1.0	0.3
		T	0.1	0.1	1.0	0.6	0.9	0.6
340	F	X	0.1	ND	1.3	3.1	3.4	1.1
		G	0.3	0.3	5.0	3.0	5.7	0.1
		T	0.2	ND	0.6	1.0	0.6	0.6
Mean ± S.E.M.		X	0.35±0.08	0.30±0.09	1.79±0.32	5.18±0.77 $p < .02$	4.08±0.47 $p < .01$	1.26±0.29
		G	0.52±0.14	0.41±0.11	2.47±0.56 $p < .01$	3.16±0.43	2.47±0.50	1.07±0.32
		T	0.49±0.11	0.41±0.11	1.70±0.48 $p < .01$	1.71±0.41	2.14±0.57	1.21±0.29

*X = xylitol; G = glucose; T = tolbutamide.
†ND = Nondetectable concentrations = < 0.78 ng./ml.; calculated as 0.

pletion of the experiments when all samples from each animal were analyzed in duplicate at once. A sample of plasma was deproteinized[6] and glucose concentrations were measured by the glucose oxidase method.[7] Immunoreactive insulin was measured in native plasma by the method of Herbert et al.,[8] utilizing either dog or monkey insulin standards.* Results were expressed as ng./ml.†

After the results were obtained, a 4.8 kg. female monkey was retested using larger doses of xylitol and glucose, with and without the addition of epinephrine, to see if it would abolish the insulinotropic effect of xylitol as epinephrine has been reported to do with glucose.[9] A total of four experiments was performed on this monkey at intervals of fourteen days. The monkey was first anesthetized as before and a solution of 0.15 M NaCl was infused at a rate of 1 ml./min. for one hour. During the next hour, one of the following solutions was infused: xylitol 300 mg./min., xylitol 300 mg. plus epinephrine 6 μg./min., glucose 300 mg./min., glucose 300 mg. plus epinephrine 6 μg./min. Saline alone was infused during the third hour. Blood samples were taken every twenty minutes and processed as described.

*Generously supplied by Dr. A. M. Fisher, Connaught Medical Laboratories, Toronto.

†Each standard had a potency of approximately 24 U./mg. Therefore, one ng. would be equal to approximately 24 μU.

RESULTS

Saline controls. In the control experiments in which

TABLE 2

Plasma insulin concentrations in monkeys (ng./ml.)

No.	Sex	Substance infused*	Minutes —15	0	5	10	30	60
32-A	M	X	0.4	0.4	0.8	0.8	0.6	0.6
		G	0.4	0.6	1.3	2.9	2.0	0.8
		T	0.2	0.2	1.9	3.5	2.2	0.8
32-B	M	X	0.1	0.1	0.6	0.1	0.8	0.8
		G	0.4	0.6	4.0	5.8	4.0	1.5
		T	0.5	0.5	2.1	3.6	2.5	1.3
27-A	F	X	ND+	0.1	0.9	0.5	0.3	0.1
		G	0.1	0.3	0.6	2.5	0.1	0.1
		T	0.1	0.1	0.5	5.0	1.0	0.1
27-B	F	X	ND	ND	1.5	0.5	0.3	0.8
		G	0.3	0.9	6.2	3.7	2.2	2.5
		T	0.5	0.8	1.3	0.8	0.9	1.2
25-A	F	X	0.1	0.6	0.5	2.4	1.4	1.0
		G	ND	0.1	1.5	3.8	1.1	0.3
		T	0.1	0.1	2.1	0.8	0.9	—
25-B	F	X	0.8	0.1	1.8	3.1	0.6	—
		G	1.0	0.8	3.4	7.4	5.5	1.2
		T	0.5	0.3	1.2	0.8	0.3	0.3
33-A	F	X	0.1	0.1	0.1	2.3	1.9	—
		G	0.3	0.3	1.9	5.3	3.6	0.3
		T	0.1	0.1	4.4	4.1	1.8	1.5
33-B	F	X	ND	ND	0.3	1.0	0.5	ND
		G	ND	0.3	13.5	10.4	2.5	0.9
		T	0.4	0.3	2.3	3.4	1.4	0.6
Mean ± S.E.M.		X	0.18±0.09	0.18±0.08	0.81±0.21	1.33±0.39 ($p < .01$)	0.80±0.20 ($p < .01$)	0.55±0.17
		G	0.31±0.12	0.48±0.10	4.05±1.49 ($p < .02$)	5.23±0.94	2.63±0.60	0.95±0.28
		T	0.34±0.04	0.30±0.09	1.98±0.41	2.75±0.60	1.38±0.26	0.83±0.20

*X = xylitol; G = glucose; T = tolbutamide.
†ND = Nondetectable concentrations = < 0.078 ng./ml.; calculated as 0.

only saline was infused, concentrations of plasma insulin and glucose were not significantly altered at any time.

Plasma insulin. Mean plasma insulin concentration increased significantly in both dogs and monkeys after infusion of xylitol, glucose or tolbutamide, but the magnitude of the increase varied with the species (tables 1 and 2; figures 1 and 2). In dogs, xylitol produced the highest mean peak insulin concentration and the highest individual peak levels in eight of ten animals. In monkeys, glucose infusion produced the highest mean peak insulin concentration and the highest individual peak levels in six of eight experiments (four animals, each tested twice with each agent). In this species, xylitol never produced higher insulin concentrations than those produced by glucose.

Plasma glucose. In dogs, plasma glucose concentrations increased by 10 per cent during xylitol infusion, but at sixty minutes, values were 12 per cent less than control levels (figure 1). Glucose infusions resulted in plasma glucose concentrations three times greater than control values, while tolbutamide infusions produced a 50 per cent decrease.

In monkeys, plasma glucose concentrations prior to infusion were lower than in dogs (55 mg./100 ml. vs 100 mg./100 ml.) (figure 2). Concentrations increased after xylitol infusion by 25 per cent. Plasma glucose increased four times after glucose infusion, while it decreased by 15 per cent after tolbutamide infusion.

Effects of epinephrine. The results of infusing a monkey with relatively large amounts of either xylitol or glucose, with and without epinephrine, are presented in figure 3. After glucose infusion, plasma insulin and glucose concentrations increased thirty-five and eighteen times, respectively. Concentrations of both were significantly higher than those after the short-term infusions with smaller doses. When glucose and epinephrine were infused simultaneously, plasma glucose concentrations increased to an even higher level than that reached with glucose alone, but plasma insulin concentrations did not

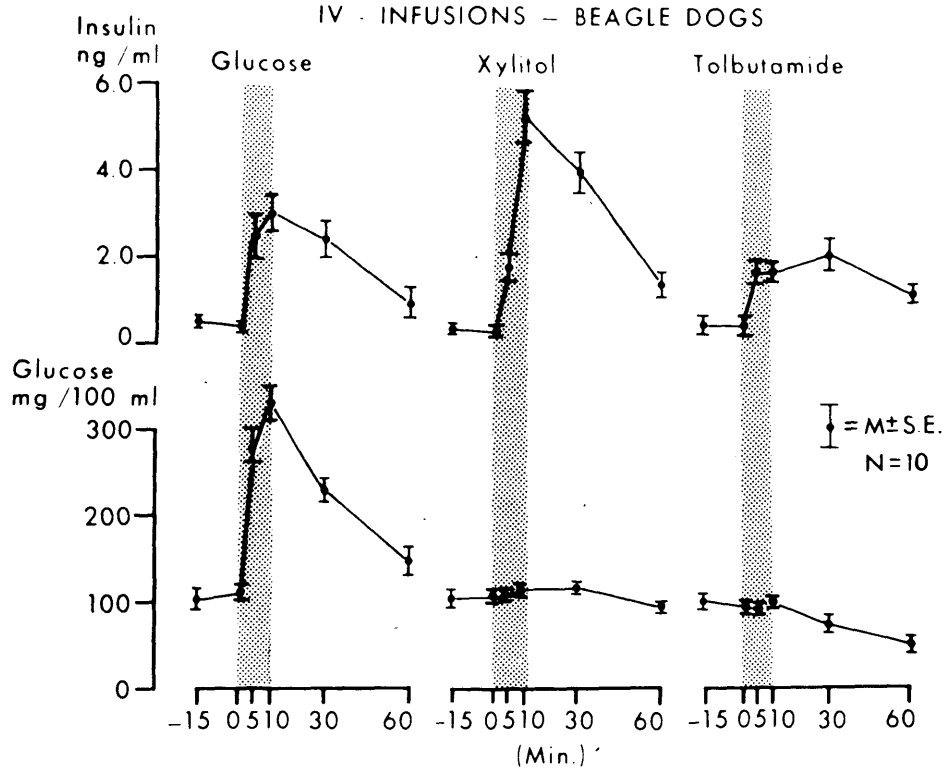

FIG. 1.

Effects of glucose, xylitol or tolbutamide infusions in dogs. Two control blood samples were taken (-15, 0 min.) and the test substance infused during the next ten minutes (shaded bar). Xylitol infusions produced the highest plasma insulin concentrations.

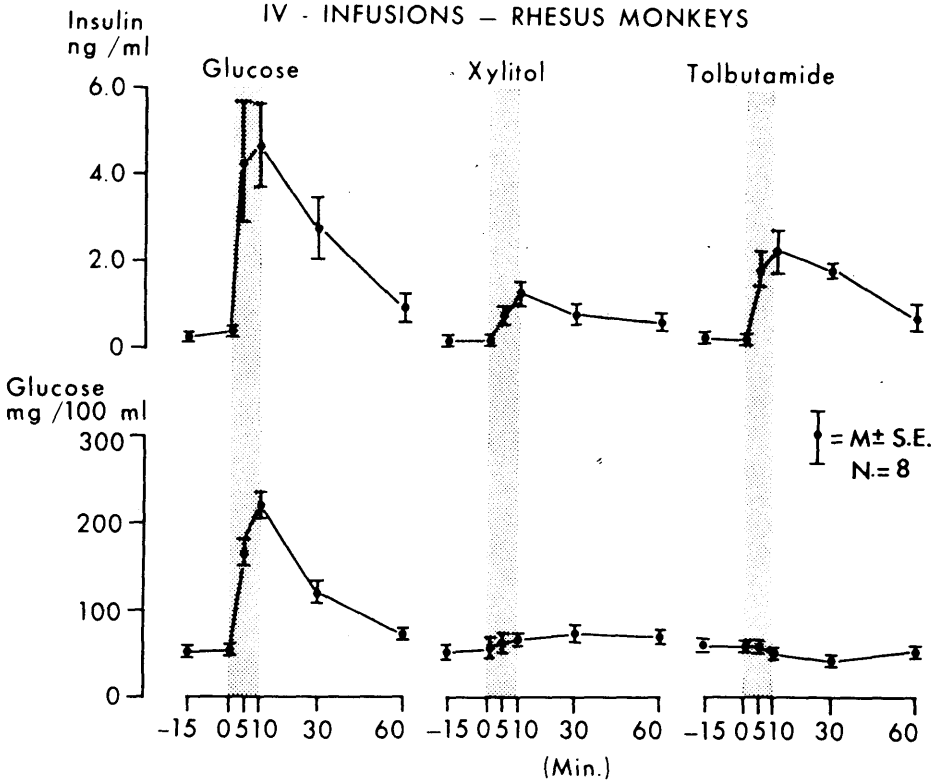

FIG. 2.

Effects of glucose, xylitol or tolbutamide infusions in Rhesus monkeys. Two control blood samples were taken (-15, 0 min.) and the test substance infused during the next ten minutes (shaded bar). Glucose infusions produced the highest plasma insulin concentrations.

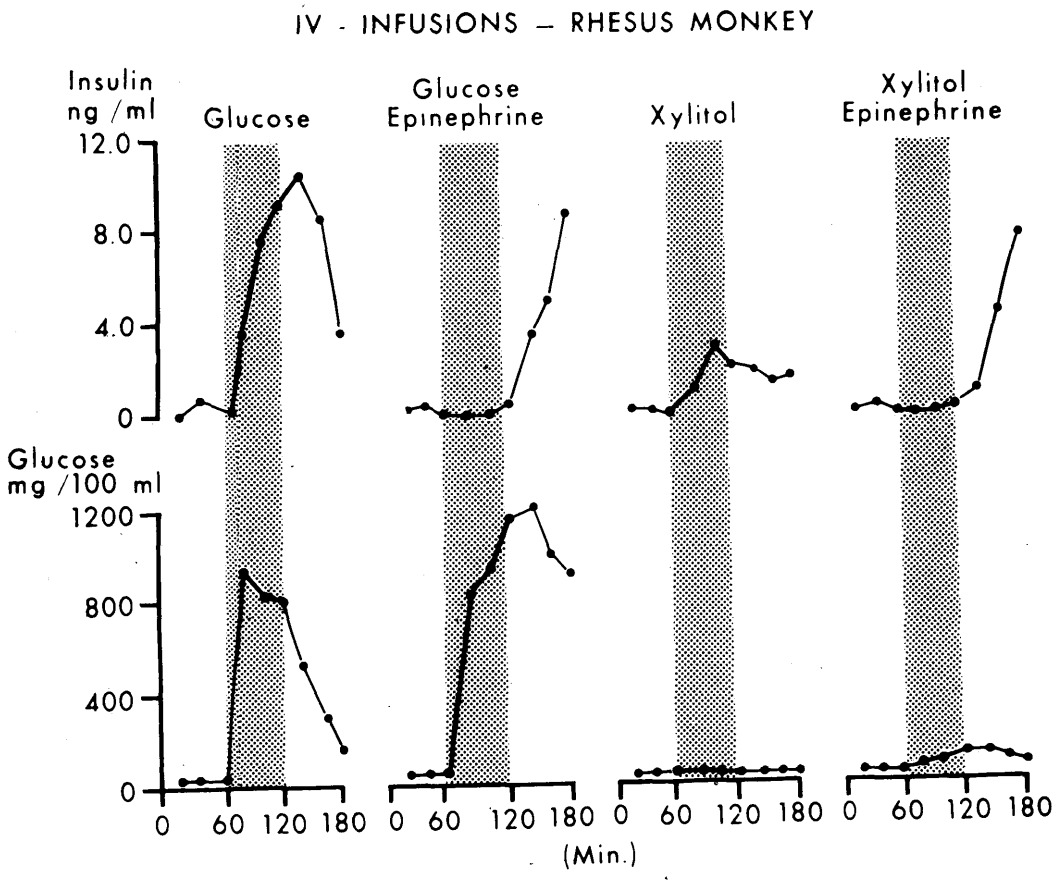

FIG. 3. Effects of either glucose or xylitol infusions with and without epinephrine in a Rhesus monkey. Saline was infused for one hour, the test substance(s) during the next hour (shaded bar), and saline alone during the third hour. Blood samples were taken every twenty minutes. Epinephrine abolished the insulinotropic effects of both glucose and xylitol.

increase until the epinephrine infusion was stopped.

During xylitol infusion, plasma insulin concentrations increased fifteen times above control levels, but the peak level was still less than half that reached after glucose infusion. When xylitol and epinephrine were infused simultaneously, glucose concentrations increased from 45 to 125 mg./100 ml., but plasma insulin concentration did not increase until the infusion was stopped, when the presumably high residual concentration of plasma xylitol and the relatively high concentration of glucose were free to stimulate the islets.

DISCUSSION

Kuzuya et al.[3] demonstrated that plasma insulin concentration in the pancreatic vein increased promptly after intravenous infusion of xylitol, suggesting that the insulinemic effect of xylitol was primarily due to the augmented secretion of insulin from the pancreas. They also found that changes in plasma insulin concentration in the femoral vein paralleled that in the pancreatic vein after either xylitol or glucose infusion. Therefore, in the present experiment we have assumed that changes in plasma insulin concentration in the saphenous vein reflected changes in the secretion of insulin in vivo.

Our experiments demonstrate marked differences in the insulinotropic potencies of xylitol, glucose and tolbutamide in dogs and monkeys. The reasons for these differences are not evident, but they illustrate again that biological mechanisms are usually qualitatively similar between species, but quantitative differences can be expected.

Results of the present investigation confirm the reports of Kuzuya et al.[1,3] and Hirata et al.[2] with respect to the high insulinotropic potency of xylitol in the dog. In monkeys xylitol produced significant increases in plasma insulin concentrations, but these increases were

never as great as those produced by comparable doses of glucose.

Although glucose is considered the most important physiologic stimulus for the release of insulin, evidence is accumulating which indicates that xylitol is also a potent insulinotropic agent in intact animals[1-4] and isolated islets of Langerhans.[10]

The exact mechanism by which glucose stimulates insulin release is still unknown, but experimental evidence suggests that a metabolic intermediate rather than glucose itself is responsible for insulin release by the beta cell.[11,12] Xylitol is known to be a metabolite in the pentose phosphate pathway.[13] Therefore, it is possible that some common metabolites produced by either xylitol or glucose, when metabolized through the pentose pathway, may trigger the release of insulin. The fact that epinephrine abolished the insulinotropic effect of both xylitol and glucose supports the possibility that both share common metabolic steps important for the release of insulin. It is possible that the pentose shunt activity is greater in the islets of dogs as compared to monkeys, but we are unaware of any evidence directly relating to this problem.

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