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Mechanisms of Glucose-Induced Hyperemia in the Jejunum (40761)[1]

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Introduction. Cardiovascular responses after a meal are characterized by an increase in blood flow through the superior mesenteric artery with little or no change in flow to other peripheral vascular beds (1). The increase in blood flow to the small intestine appears to be confined to that region of the intestine which is exposed to chyme (2), and the constituents of chyme responsible for the hyperemia are the digested products of food (3). Glucose, a major product of carbohydrate digestion, has consistently been shown to increase blood flow when placed into the lumen of the small intestine (3–5). The mechanism underlying the hyperemia, however, is not clear. In order to examine the possibility that the hyperemia may be related to glucose absorption and local metabolism, vascular effects of glucose, and its synthetic analogs, 3-0-methyl glucose (3-MG), and 2-deoxy glucose (2-DG), (Sigma Chemical Co.), were compared in the present study. It has been shown that glucose is both actively absorbed and metabolized, 3-MG is actively absorbed but not metabolized (6, 7), and 2-DG is neither absorbed nor metabolized by the small intestine (6). Since bile, a natural constituent of chyme, has been shown to markedly enhance the hyperemic effect of digested food (3), the present study also examines whether bile would enhance the vascular effect of glucose as well as its synthetic analogs.

Methods. Mongrel dogs (15–25 kg) of either sex were fasted for 24 hr, anesthetized with sodium pentobarbital (30 mg/kg, i.v.), and ventilated with a positive pressure Harvard respirator to ensure normal arterial pH (7.38–7.43). A loop of the jejunum about 30 cm distal to the ligament of Treitz was exteriorized and divided into two segments, each drained by a single vein (3, 4). After administration of heparin sodium (6 mg/kg), these veins were cannulated for measurement of venous outflow. The outflow was directed to a reservoir and the blood was returned to the animal through a femoral vein at a rate equal to the venous outflow. A rubber tube was placed into the lumen of each segment for the introduction and withdrawal of solutions to be tested. At all other times, the tubes were connected to Statham pressure transducers (P23 GB) to monitor intraluminal pressure. Both ends of each segment were tied and the mesentery cut to exclude collateral flow and to prevent bleeding. The segments were covered with a plastic sheet and kept at 37° with a heat lamp. Systemic arterial pressure was continuously monitored through a femoral arterial cannula.

The protocol for the experiments consisted of three 15-min periods: precontrol, test, and postcontrol. In the pre- and postcontrol periods, both segments contained 10 ml normal saline while in the test period one segment contained 10 ml of glucose solution and the other contained 10 ml of either 3-MG or 2-DG solution so that their vasoactivities could be compared. The glucose solutions were made as follows: One part of normal saline or bile (aspirated from the animal's gallbladder prior to the experiments) was added to two parts of a solution containing 300 m*M* of glucose, 3-MG or 2-DG. These glucose solutions were isotonic, at pH 6.8–7.2, and were kept at 37°.

In each 15-min period, venous outflows from both segments were simultaneously collected in graduated cylinders in 3-min samples with a 1-min interval in between collections. The volume of blood was determined and the blood was poured into the reservoir. After each period, the luminal contents were withdrawn, and the lumen was gently and thoroughly washed with normal saline.

In another series of experiments only one

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segment was prepared from the jejunal loop as described above. In addition to venous outflow, oxygen consumption and glucose absorption were measured during luminal placement of glucose + bile, 3-MG + bile, 2-DG + bile, or bile alone. The arteriovenous oxygen (A-V O_2) difference was continuously monitored by perfusing femoral arterial blood and a portion of the jejunal venous outflow through an A-V O_2 difference analyzer (No. 1020, A-Vox Systems, San Antonio, Tex.). The analyzer was previously calibrated with a Lex-O_2-Con-TL (Lexington Instruments, Waltham, Mass.). Arterial and venous samples were obtained before and at 5, 10, and 15 min after placement of test solutions for determinations of plasma glucose and 2-DG (glucose oxidase method) (8) or 3-MG concentration (Somogyi and Nelson method) (8). Oxygen consumption of the jejunal segment was calculated as the product of A-V O_2 difference and venous outflow. Glucose absorption was determined by the product of A-V glucose difference and venous outflow. The protocol for the experiments in this series was essentially similar to those of the first series.

Student's *t* test modified for paired comparison was used for all statistical analyses where appropriate. The Student's group *t* test for equal variance with unpaired observations was used to compare the vascular and metabolic effects as well as absorption rates of the three glucoses. Statistical significance was set at *P* values less than 0.05.

Results. Luminal placement of any of the test solutions did not significantly alter systemic arterial pressure (123 ± 2 mm Hg, mean ± SEM) or luminal pressure (2.6 ± 0.3 mm Hg). After the jejunal segment was exposed to a test solution, venous outflow increased gradually and reached a steady state within 5 to 10 min and this lasted about 20 min. Therefore, the blood flow values taken at the 12- to 15-min period were used for expressing and analyzing the data.

As shown in Fig. 1, glucose and 3-MG in the absence of bile significantly increased venous outflow by 8.9 and 4% of precontrol respectively; the difference of 5.0% was statistically significant ($P < 0.05$). Addition of bile markedly enhanced the hyperemic effect of glucose (17.2% above control) but not 3-MG (4.3%). The difference in their hyperemic effect thus increased to 13.3%. Figure 2 shows that while glucose significantly increased blood flow, 2-DG did not alter flow either with or without bile. Thus, of the three glucoses, only glucose and 3-MG were capable of increasing blood flow with the hyperemic effect of glucose being greater than that of 3-MG. The sec-

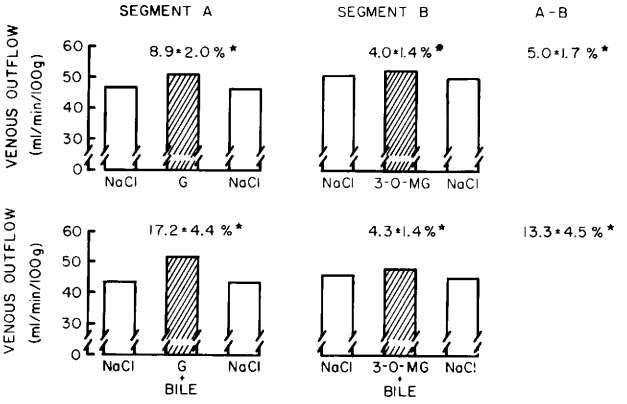

FIG. 1. Comparison of vascular effects of glucose (G) and 3-*O*-methyl glucose (3-MG) with or without bile, in double jejunal segments ($N = 6$). Values above bars indicate percentage change from precontrol. A − B = Difference in changes produced by the two paired solutions. Asterisks indicate that the values are significant at $P < 0.05$. Thus, G or 3-O-MG significantly increased blood flow but G produced a greater increase in blood flow than 3-O-MG does with or without bile.

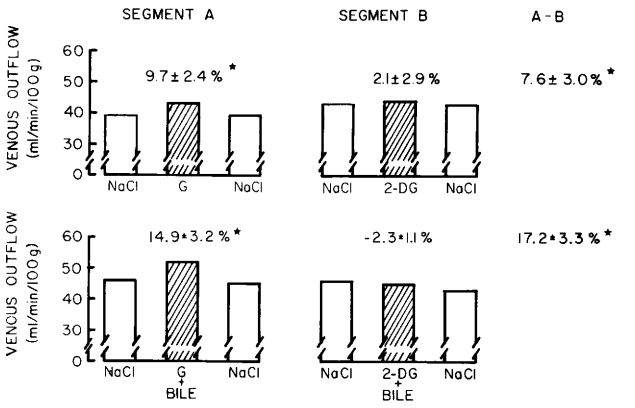

FIG. 2. Comparison of the vascular effects of glucose (G) and 2-deoxy glucose (2-DG) with or without bile, in the double jejunal segments ($N = 7$). Values above bars indicate percentage change from precontrol. A − B = Differences in changes produced by the two paired solutions. Asterisks indicate that the values are significant at $P < 0.05$. Thus, G with or without bile increases blood flow but 2-DG does not significantly alter blood flow.

ond series of experiments were then performed to determine if the differences in the vascular effect were related to absorption and local oxygen consumption.

As shown in Fig. 3, in the presence of bile, both glucose and 3-MG increased blood flow but only glucose significantly increased oxygen consumption. The increase in oxygen consumption was primarily due to an increase in blood flow rather than oxygen extraction since A-V O_2 difference was not altered. The hyperemic effect of glucose was again significantly greater than that of 3-MG ($P < 0.05$). However, there was no difference between the absorption rates of glucose and 3-MG. Bile alone or 2-DG plus bile did not alter blood flow or oxygen consumption. There was no hexose absorbed when saline (during control periods), bile, or 2-DG were in the lumen.

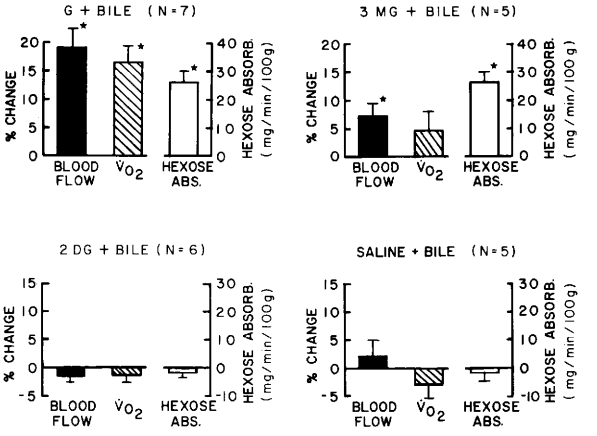

FIG. 3. Percentage change in blood flow and oxygen consumption from precontrol after luminal placement of glucose (G), 3-*O*-methyl-glucose (3-MG), and 2-deoxy-glucose (2-DG), with bile, and bile alone. Control blood flow was 42.5 ± 2.1 ml/min/100 g and V_{O_2} was 1.50 ± 0.05 ml/min/100 g. HEXOSE ABS. denotes the rate of absorption of the hexose placed into the lumen. During the placement of saline + bile, the rate of glucose absorption was determined. Asterisks indicate that the values are significant at $P < 0.05$.

Discussion. It is well established that the presence of glucose at concentrations ranging from 150 to 3000 m*M* in the jejunal lumen increases local blood flow (3–5, 9). In order to elucidate some of the mechanisms involved in the hyperemia, the present study compared the vascular and metabolic effects as well as absorption rates of glucose and its synthetic analogs, 3-MG and 2-DG. The three glucoses have different absorption and metabolic characteristics.

Both glucose and 3-MG, which were absorbed from the lumen, significantly increased local blood flow but the nonabsorbable glucose, 2-DG, did not (Fig. 3). This appears to indicate that the glucose induced hyperemia is probably related to its absorption. Other studies also support this thesis. It has been shown that a 20% glucose solution (1200 mOsm/liter) in the jejunal lumen increases local blood flow but a solution of nonabsorbable substance, polyethylene glycol, with the same osmolarity does not (4). Furthermore, the increased jejunal blood flow during the presence of food or hypertonic glucose in the lumen is confined to the mucosal layer (2, 9). The mucosa is the site for transmembrane transport of water, electrolytes, and other nutrients. Thus, the postprandial intestinal hyperemia seems to be a functional hyperemia related to the absorption of nutrients.

The absorption rate of 3-MG is similar to that of glucose but the hyperemic effect of 3-MG is significantly less than that of glucose (Figs. 1 and 3). This appears to indicate that absorption is not the sole contributing factor for the hyperemia. *In vitro* studies have shown that glucose is both absorbed and metabolized but 3-MG is absorbed but not metabolized in the small intestine (6, 7). This finding is similar to that of the present study which shows that glucose increases but 3-MG does not significantly increase local oxygen consumption (Fig. 3). An increase in local oxidative metabolism, therefore, may be another contributing factor for the glucose-induced hyperemia.

A recent study has shown that bile markedly enhances the hyperemic effect of digested food in the canine jejunum (3). Thus, another purpose of the present study was to examine whether bile would enhance the vascular effect of glucose and its synthetic analogs. As shown in Figs. 1 and 2, while bile significantly enhances the vascular effect of glucose, it does not influence the vascular effect of 3-MG and 2-DG. Although the underlying mechanisms are unknown, it does not appear to be due to the vascular effect of bile since bile alone in the lumen does not alter local blood flow (Fig. 3). Our preliminary studies have also shown that while bile enhances the hyperemic effect of glucose in the jejunal lumen (10), it does not influence the rates of glucose absorption and oxygen consumption (11). Thus, the influence of bile on the glucose-induced hyperemia does not seem to be related to glucose absorption or oxidative metabolism. Since local nerves and gastrointestinal hormones have been proposed to mediate postprandial intestinal hyperemia (4, 9, 12, 13), bile may influence the effect of glucose on local nerves and/or the release of local vasodilator substances. However, because bile influences only the effect of glucose and not 3-MG or 2-DG, the intermediate step appears to be structure specific.

Summary. The present study compared the effects of placement of three glucose analogs into the jejunal lumen, with or without bile, on local blood flow, oxygen consumption, and glucose absorption. Both glucose and 3-*O*-methyl glucose were absorbed and increased local blood flow when placed into the lumen, 2-deoxy glucose was not absorbed and did not alter local blood flow. Glucose increased but 3-*O*-methyl glucose did not alter oxygen consumption and the former produced a greater hyperemia than the latter. The study thus suggests that the hyperemic effect of glucose in the jejunal lumen is, at least in part, related to glucose absorption and an increase in oxidative metabolism. Of the three glucoses, only the vascular effect of glucose was influenced by bile. Although the underlying mechanisms of this effect of bile are unknown, the study suggests that the mechanisms require structure specificity.

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