The Effect of Bran on Glucose Kinetics and Plasma Insulin in Non-insulin-dependent Diabetes Mellitus

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Experiments were carried out on two groups of diabetic patients treated (1) by diet alone (group A) and (2) by diet and oral agents (group B), the latter being discontinued 3 days before each test. All patients were tested twice. To measure rates of glucose metabolism, $^3$H-3-glucose was infused before and during a standard 3-h 50-g oral glucose tolerance test. $^{14}$C-1-glucose was added to the glucose solution and the percentage of ingested glucose that appeared in peripheral blood was calculated. Bran improved glucose tolerance only in group B patients by delaying the peripheral appearance of ingested glucose but had no effect on glucose absorption in group A. In contrast, patients in group A showed a marked reduction in their insulin response when bran was mixed with the glucose. Despite this reduction, glucose tolerance, the metabolic clearance rate (MCR) of glucose, and all other rates measured were unaffected by bran. Thus we conclude that in patients adequately controlled by diet alone, the effect of insulin was potentiated when bran was ingested, but the mechanism involved remains obscure. DIABETES CARE 3:520-525, JULY-AUGUST 1980.

Reports of a low incidence of diabetes mellitus among people who eat a diet rich in "fiber" have led to many attempts to examine the effects of dietary fiber on glucose tolerance. There appears to be general agreement between investigators that in diabetic patients who retain some insulin secretory capacity, glucose tolerance improves when a variety of dietary fiber, including bran, is added to a carbohydrate load.

Some studies have demonstrated that this improvement is associated with a smaller increase in plasma insulin, thus raising the possibility that fiber can increase insulin sensitivity. However, an alternative explanation may be that fiber reduces or delays glucose absorption from the gut and, in so doing, puts less demand on the $\beta$-cell.

The purpose of these experiments was to examine quantitatively to what extent either of the above mechanisms contribute to the changes in plasma glucose and insulin seen when glucose is ingested, either with or without additional fiber. Therefore, the questions asked were (1) could the addition of bran to ingested glucose increase the sensitivity to endogenously released insulin? and (2) does bran delay the absorption of glucose from the gut?

SUBJECTS

Informed consent was obtained from two groups of non-insulin-dependent diabetic patients attending the diabetic clinic at the Ottawa Civic Hospital.

Group A: patients treated by diet alone. Group A contained seven men who ranged in age from 33 to 67 yr (mean 46 ± 4.6 yr), maintained on a diet consisting of 44% carbohydrate, 36% fat, and 21% protein. All cases their diabetes had been stable for at least 6 mo before investigation. They were otherwise healthy and not obese, with normal fasting plasma glucose concentrations.

Group B: patients treated with diet and oral agents. In this group were four men and three women, ranging in age from 54 to 74 yr (mean 57 ± 3.5 yr). Three patients had diabetes for 10 yr or longer. All were taking some medication in addition to sulfonylurea, which was discontinued 3 days before each test.

MATERIAL AND METHODS

Procedure. The experiments were carried out after an overnight fast with the subjects warm, relaxed, and semisupine.
At the start of the experiment 10 μCi 3H-3-glucose was injected via a cannula introduced into an antecubital vein. This was followed immediately by an infusion for 4.25 h of 0.16 μCi/min 3H-3-glucose into the same vein. Blood samples were withdrawn from a contralateral antecubital vein at 30, 40, 50, and 60 min after the priming injection. At this time the subjects drank 125 ml of flavored glucose solution (J. T. Baker Diagnostics) containing 50 g glucose labeled with 50 μCi 14C-1-glucose. This solution was ingested either alone or mixed with 50 g unprocessed wheat bran. Further blood samples were withdrawn at 70, 90, 110, 120, 150, 170, 190, 210, 220, 240, and 255 min. Each patient was tested twice, once with glucose and bran and once with glucose alone. The order of the tests was alternated. On average, it took 4 min to consume the glucose load, and the time was identical for both tests on the same patient. The tests were 1 wk apart for group A and 2 wk apart for group B, who resumed their medication in the intervening period.

Not all patients became glycosuric, but urine was collected at the beginning and end of the experiment. The rate of glycosuria was estimated from the latter sample and used to correct the overall rate of disappearance of glucose for glucose excretion.

Three other patients, whose diabetes was controlled by diet, received a 2-h intravenous infusion of glucose equivalent to the amount of glucose that appeared in peripheral blood (approximately 20 g) during 2 h of the experiments described above (i.e., between t = 60 and 180 min). Twenty minutes before the start of the infusion, 125 ml of water, either alone or mixed with bran, was ingested.

**Chemical methods.** Glucose-blood samples were collected in cooled glass tubes containing Na fluoride and oxalate and centrifuged immediately after withdrawal. The concentration of glucose in plasma, urine, and the glucose drink was measured enzymatically in a Beckman Glucose Analyzer. The rate of glucosuria was estimated from the latter sample and used to correct the overall rate of disappearance of glucose for glucose excretion.

**Hormones.** Plasma IR1 was determined by the method of Hales and Randle using a kit purchased from Amersham-Searle Ltd. with human insulin as the reference standard. Plasma IRGIP (immunoreactive gastric inhibitory polypeptide) was measured by a specific radioimmunoassay using antibody G.P.-24.

**Calculations.** Polynomial curves were fitted to describe the time courses of the plasma glucose concentration (mmol/L) and its specific activity (SA) as dpm-μmol−1 with respect to both 3H and 14C glucose. The integrals of these curves were calculated between 70 and 255 min by standard analytical methods. The rates of appearance (Ra) and disappearance (Rd) of glucose as μmol-min−1·kg−1 were calculated by the equation of Steele et al., as modified by Cowan and Hetenyi. The metabolic clearance rate of glucose (MCR), ml·min−1·kg−1, was then calculated as the ratio of the rate of disappearance of glucose to its plasma concentration. From the rate of appearance of glucose into the circulation calculated from the SA (3H-glucose) time curve and from the parameters of the 14C SA time curve, the rate of input of 14C into the circulation (dpm·min−1) was calculated. The rate of appearance of glucose originating from the gut into the peripheral circulation was determined from the specific activity of the ingested glucose and the rate of appearance of 14C in peripheral blood.

**Polynomial curves were also fitted to describe the time course, from 70 to 255 min, of the increment in the plasma glucose concentration, the overall rate of appearance of glucose, the rate of appearance of glucose originating from the gut, and the MCR of glucose. These curves were integrated as described above to obtain the area under each curve between these time limits.**

**RESULTS**

The outcome of a single experiment is shown in Figure 1. This figure shows the specific activity of plasma glucose with respect to both 3H and 14C before and after the ingestion of 50 g of glucose in patient no. 2 in group A.

The mean incremental changes in the concentration of plasma glucose after the ingestion of 50 g glucose with and without bran are shown for both groups of patients in Figure 2. In group A patients glucose tolerance, as measured by the area under the plasma glucose concentration versus time curve, was not changed significantly, although an improvement was noted in three out of the seven patients. Results of experiments of identical design, carried out in group B patients, were analyzed by a three-way analysis of variance. The effect of bran in improving glucose tolerance was significant (F = 13.69, P < 0.025).

The rise in plasma concentration of insulin in response to glucose was considerably decreased by bran in group A patients. Increments from the baseline level of plasma IR1 are

\* The concentration observed at time equals t minus the mean level for t > 60 min.
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A DIET ALONE

FIG. 2. Increments in the concentration of plasma glucose after the ingestion of 50 g glucose either with (O—O) or without (●—●) 20 g of bran at t = 60. Upper panel, group A; lower panel, group B. Average values for seven patients are shown for each group; bars denote SEM. Starting plasma glucose concentrations are group A, control: 100.6 mg/dl (5.6 mmol/L^-1); bran: 95.4 ± 2.2 mg/dl (5.3 mmol/L^-1). Group B, control: 183.6 ± 15.8 mg/dl. Shown in Figure 3. A three-way analysis of variance revealed significantly lower IRI levels in group A when the patients ingested glucose mixed with bran rather than glucose alone (F = 36.7, P < 0.005). The interaction between patients and treatment (with or without bran) was also significant (F = 17.8, P < 0.005), indicating that at least in this respect (i.e., their response to bran), this group of patients was not homogeneous.

As shown in Table 1, changes in the concentration of IRGIP in the plasma, induced by the glucose load, were not

shown in Figure 3. A three-way analysis of variance revealed significantly lower IRI levels in group A when the patients ingested glucose mixed with bran rather than glucose alone (F = 36.7, P < 0.005). The interaction between patients and treatment (with or without bran) was also significant (F = 17.8, P < 0.005), indicating that at least in this respect (i.e., their response to bran), this group of patients was not homogeneous.

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### Table 1

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group A (N = 7)</th>
<th>Glucose infusion (N = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>Bran</td>
<td>51</td>
</tr>
<tr>
<td>Basal level</td>
<td>(896 ± 244)</td>
<td>(617 ± 295)</td>
</tr>
<tr>
<td>110</td>
<td>±114</td>
<td>±43</td>
</tr>
<tr>
<td>120</td>
<td>±373</td>
<td>±77</td>
</tr>
<tr>
<td>130</td>
<td>±313</td>
<td>±33</td>
</tr>
<tr>
<td>140</td>
<td>±381</td>
<td>±50</td>
</tr>
<tr>
<td>150</td>
<td>±295</td>
<td>±15</td>
</tr>
<tr>
<td>160</td>
<td>±226</td>
<td>±36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group B (N = 7)</th>
<th>No bran</th>
<th>Basal level (1070 ± 432)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>Bran</td>
<td>69</td>
<td>50</td>
</tr>
<tr>
<td>Basal level</td>
<td>(1038 ± 235)</td>
<td>(697 ± 28)</td>
<td>±50</td>
</tr>
<tr>
<td>80</td>
<td>±174</td>
<td>±203</td>
<td>±69</td>
</tr>
<tr>
<td>90</td>
<td>±329</td>
<td>±298</td>
<td>±84</td>
</tr>
<tr>
<td>100</td>
<td>±381</td>
<td>±359</td>
<td>±129</td>
</tr>
<tr>
<td>110</td>
<td>±245</td>
<td>±287</td>
<td>±204</td>
</tr>
<tr>
<td>120</td>
<td>±296</td>
<td>±433</td>
<td>±295</td>
</tr>
<tr>
<td>130</td>
<td>±278</td>
<td>±384</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2
Incremental changes in plasma glucose and IRI during the 125-min glucose infusion (i.v.)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>70</th>
<th>90</th>
<th>120</th>
<th>130</th>
<th>145</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Glucose (mmol/L⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No bran</td>
<td>-0.45 ± 0.04</td>
<td>-0.55 ± 0.06</td>
<td>-0.22 ± 0.63</td>
<td>0.68 ± 0.33</td>
<td>0.68 ± 0.28</td>
<td>1.2 ± 0.36</td>
<td>1.5 ± 0.34</td>
<td>1.7 ± 0.22</td>
<td>1.8 ± 0.25</td>
<td>1.8 ± 0.18</td>
</tr>
<tr>
<td>With bran</td>
<td>-0.27 ± 0.07</td>
<td>-0.5 ± 0.15</td>
<td>0.47 ± 0.35</td>
<td>1.0 ± 0.21</td>
<td>1.2 ± 0.26</td>
<td>1.5 ± 0.3</td>
<td>1.7 ± 0.15</td>
<td>1.9 ± 0.14</td>
<td>2.0 ± 0.06</td>
<td>2.0 ± 0.06</td>
</tr>
</tbody>
</table>

| Δ IRI (µU/ml⁻¹) |    |    |    |    |    |    |    |      |      |     |
|----------------|----|----|----|----|----|----|----|      |      |     |
| No bran        | -1.36 ± 0.47 | 1.6 ± 0.42 | 1.8 ± 0.31 | 0.56 ± 0.54 | 2.2 ± 0.42 | 3.1 ± 1.0 | 4.7 ± 3.5 | 7.8 ± 6.2 | 5.1 ± 4.2 | 2.9 ± 1.4 |
| With bran      | -0.77 ± 1.5 | -1.1 ± 1.2 | 0.44 ± 2.4 | 2.65 ± 2.6 | 4.5 ± 2.6 | 4.1 ± 2.7 | 6.6 ± 1.4 | 3.1 ± 5.4 | 4.0 ± 3.1 | 2.7 ± 2.1 |

Bran ingested at t = 0. Glucose infusion started at t = 20.
Basal concentrations: glucose, 9.73 ± 2.7 (no bran) and 9.83 ± 2.9 (bran). Insulin, 22.2 ± 3.7 (no bran) and 21.3 ± 3.7 (bran).

altered by the presence of bran in the gut in either group of patients.

In the three patients who received an intravenous glucose infusion after ingesting bran, no difference due to the bran could be detected in either plasma glucose or plasma IRI concentration during the glucose infusion (Table 2). The plasma concentration of IRGIP did not rise in response to infused glucose whether or not bran was ingested (Table 1).

The rate of appearance of glucose from all sources into the circulation before and after the ingestion of glucose is shown in Figure 4. In the first hour this rate (calculated from the plasma SA time curve of 3H-glucose) represents hepatic glucose production. Patients in group B had higher basal rates of glucose production (13.4 ± 1.3 µmol·min⁻¹·kg⁻¹) than patients in group A (9.5 ± 0.55 µmol·min⁻¹·kg⁻¹) (t = 2.51, P < 0.05). The rate at which glucose from the gut appeared in peripheral blood [as calculated from the SA (t) curve of 14C-glucose] is also shown. The difference between the two rates after the glucose drink represents the rate of hepatic glucose release. Neither rate was changed significantly by

FIG. 4. Rates of appearance of all glucose from all sources (total Ra) and of glucose from the gut (gut Ra) before and after the ingestion of 50 g glucose with (O or △) or without (● or ▲) 20 g of bran at t = 60 min. Upper panel, group A; lower panel, group B. Average values for seven patients are shown for each group; bars denote SEM. Where SEM overlap, bars are not shown.
I. Glucose tolerance. did not improve glucose tolerance in patients controlled by diet alone. These patients evidently were able to maintain normal glucose homeostasis. On the other hand, whether or not bran was mixed with the drink. Therefore, we conclude that the reduced responsiveness of the β-cells to elevated plasma glucose must be mediated by some humoral or neural mechanism invoked by the presence of bran in the gut.

In group A, bran had no effect on the percentage of ingested glucose that appeared in peripheral blood during 185 min following glucose ingestion. In group B patients 75.9 ± 4.6% of ingested glucose appeared peripherally during this time. The addition of bran, however, reduced this percentage marginally to 61.1 ± 5.2 in these patients, a value similar to that found in group A.

The MCR of glucose in the first hour before the ingestion of glucose was similar in both the control and bran experiments. However, this rate was significantly lower in group B patients (1.3 ± 0.06 ml·kg⁻¹·min⁻¹) than in group A (1.7 ± 0.11 ml·kg⁻¹·min⁻¹) (* = 4.32, P < 0.005). As shown in Table 3, in neither group of patients did bran alter the mean glucose clearance (integral of MCR) over the 185-min period following the ingestion of glucose.

**DISCUSSION**

Glucose tolerance. The addition of bran to ingested glucose did not improve glucose tolerance in patients controlled by diet alone. These patients evidently were able to maintain relatively normal glucose homeostasis. On the other hand, in the patients who were hyperglycemic to start with, bran improved glucose tolerance significantly.

Insulin response to the glucose load. As found in normal men,12,13 the unaltered glucose tolerance of patients in group A was achieved with a smaller increment in plasma IRI. The rate (μU/min⁻¹) at which insulin is secreted, at any time, is the product of the MCR (ml/min⁻¹) of insulin and the concentration of plasma insulin at that time. Since the MCR of insulin by liver is relatively constant in the basal state, changes in serum levels provide a reasonable approximation of changes in pancreatic secretion. However, we cannot exclude the possibility that bran increases portal blood flow, thereby decreasing serum insulin because of increased hepatic extraction.14,15

The reason for the decreased insulin response is not clear. If there were a significant delay in absorption of glucose from the gut, then we should expect to see such a reduction in insulin release. However, glucose from the gut appeared in peripheral blood at the same rate in this group of patients, whether or not bran was mixed with the drink. Therefore, we conclude that the reduced responsiveness of the β-cells to elevated plasma glucose must be mediated by some humoral or neural mechanism invoked by the presence of bran in the gut.

Apparently, in order to achieve the reduction in the insulin response, bran and glucose have to be present in the gut simultaneously, since no alteration in insulin response was noted in the patients in whom glucose was infused intravenously, after the ingestion of bran and water. Therefore, it appears unlikely that bran diminishes the release of the gut hormones known to be released by glucose and which increase the secretion of insulin. Certainly, the changes in concentration in the blood of one such hormone, GIP, were unaffected by bran.

Absorption of the glucose load. In our patients whose diabetes was controlled by diet alone, 67.3 ± 4.5% of the ingested glucose was recovered at the site of blood sampling (an antecubital vein), whereas 75.0 ± 4.6% was recovered in patients formerly on oral agents. These recoveries of ingested glucose in the peripheral circulation are less than the 90 ± 4% reported by Radziuk et al. in normal subjects, but the larger retention of glucose by the subjects whose diabetes was well controlled (group A) agrees with the generally accepted view of a larger retention of glucose by the liver in the presence of insulin.16

In the patients in whom medication had been discontinued (group B), bran initially delayed the peripheral appearance of glucose from the gut, so that in 185 min following the glucose load 61.1 ± 5.2% of ingested glucose appeared, compared with the 75.0 ± 4.6% in the absence of bran. This delay in glucose absorption probably accounts for the small improvement in glucose tolerance seen in the patients of group B. The reason for the difference in glucose absorp-

**TABLE 3**

Appearance of glucose from all sources and from the gut and the integrated metabolic clearance rate

<table>
<thead>
<tr>
<th></th>
<th>Appearance from all sources (mmol)</th>
<th>Appearance from the gut (mmol)</th>
<th>Percentage suppression of endogenous glucose production (70 &lt; t &lt; 255 min)</th>
<th>Percentage of ingested glucose appearing in peripheral blood (70 &lt; t &lt; 255 min)</th>
<th>MCR integrated (70 &lt; t &lt; 255 min) (ml·kg⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Control Bran</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SEM</td>
<td></td>
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<tr>
<td>223 ± 7.9</td>
<td>218 ± 22.2</td>
<td>172 ± 10.8</td>
<td>163.4 ± 13.3</td>
<td>59 ± 5.8</td>
<td>55.7 ± 11.5</td>
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<td></td>
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<td></td>
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<tr>
<td>Diet plus oral agents Bran</td>
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<td></td>
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<td></td>
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<tr>
<td>Mean ± SEM</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>274 ± 17</td>
<td>251 ± 14</td>
<td>201 ± 15</td>
<td>163 ± 12</td>
<td>58 ± 11</td>
<td>53 ± 7</td>
</tr>
</tbody>
</table>

H. H. HALL, T. M. BOLTON, AND G. HETENYI, JR.
tion between the two groups is not clear and may be due to differences either in absorption of glucose from the gut or in retention of glucose by the liver.

The suppression of hepatic glucose production was not affected by the ingestion of bran in either group of patients. Its calculated value in the patients controlled by diet alone, 59.0 ± 5.8%, was not significantly different from the 66.0 ± 6% found by Radziuk et al.17 in normal subjects. Remarkably, the degree of hyperglycemia did not affect the extent to which hepatic glucose production was reduced by the glucose load. This indicated that the effects of factors other than insulin, be they hormones or the cellular response to excess glucose, are able to compensate for the lack of mobilization of insulin, believed to mediate the decrease in glucose production in response to infused glucose.18-20

Insulin sensitivity. We did not measure tissue sensitivity to insulin directly. However, the magnitude of the metabolic clearance rate of glucose in the intact organism is largely insulin dependent.21 Thus, group B patients, whose insulin response was poor, had significantly lower glucose clearance rates than group A patients. In group A the MCRs integrated over 185 min, following the glucose drink for both insulin dependent.

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sponse was poor, had significantly lower glucose clearance

rates than group A patients. In group A the MCRs inte-

grated over 185 min, following the glucose drink for both

control and bran studies, were remarkably close, despite the

considerably reduced increment in plasma insulin when bran

was ingested. These experiments suggest that sensitivity of

peripheral tissues to insulin may be increased by the presence

of bran in the gut, although they offer no explanation as to

the mechanism involved.

ACKNOWLEDGMENTS: The authors are indebted to Dr. S. Raman for his advice and help with the analysis of variance of the data and to Dr. J. Brown at the University of British Columbia for measuring plasma GIP concentration. We are also grateful for the highly skilled technical assistance of R. A. Layberry and Heather Rowell. The secretarial assistance of Jane McNeill is gratefully acknowledged.

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REFERENCES