The Influence of Sweetener Solutions on the Secretion of Insulin and the Blood Glucose Level

The low calorie sweeteners aspartame, acesulfame-K, cyclamate and saccharin are used to sweeten energy-reduced drinks and foods. They provide the expected sweet taste while reducing the energy content compared to products sweetened with sucrose. This reduction of calories should assist consumers of these products in attempting to reduce or maintain bodyweight.

The role of low calorie sweeteners in weight management was questioned by BLUNDELL et al. following a survey in which an increase was observed in the subjective feelings of hunger of test subjects given aspartame in water [1,2]. In another experiment, an increased intake of food was observed after the consumption of yoghurt sweetened with saccharin [3]. These results were widely discussed, although BLUNDELL himself could not confirm his previous observations in a second study with aspartame in water solutions [4]. In one of his papers [3], BLUNDELL attempted to explain his observation by suggesting that sweeteners cause a cephalic insulin release that would decrease the blood glucose level and cause the observed feelings of hunger. We are not aware of physiological investigations into possible underlying mechanisms.

A number of studies dealing with similar questions have been published in recent years. The majority of experimental studies have shown a reduction in energy intake and bodyweight following the substitution of sucrose by low calorie sweeteners. However, in some studies, particularly the most recent ones, no effect was found on either energy intake or bodyweight [5-8]. Relatively few experimental data have supported the suggestion by BLUNDELL [3] that a cephalic insulin response was the physiological cause of his observations. In one experiment [9], a brief increase in the insulin level was detected; in other experiments [10,11], no change in the insulin level was observed. These differences may be partly due to the fact that low calorie sweeteners were given in foods and drinks which themselves could be responsible for a cephalic secretion of insulin [9].

Stimulation of feelings of hunger by low calorie sweeteners alone seems unlikely. Data presently available on the influence of low calorie sweeteners on the secretion of insulin and the level of blood sugar are insufficient to prove the existence of a cephalic insulin secretion and a resulting change in the blood glucose level.

The aim of the present experiment was to obtain data, under controlled conditions, which were independent of the influence of other substrates normally present in food and drink.

The objective was to determine whether giving aqueous solutions of the low calorie sweeteners aspartame, acesulfame-K, cyclamate and saccharin (all licensed in the Federal Republic of Germany under the food law) to healthy subjects would influence the secretion of insulin which could result in changes in the level of blood sugar.
Methods

Subjects

Fourteen healthy subjects were included in the study test group which consisted of eight women and six men aged between 19 and 52. The criteria for inclusion in the study were: an oral test of glucose tolerance with normal results for glucose tolerance; blood glucose on an empty stomach < 6.6 mmol/litre and 2-hours concentration < 6.6 mmol/litre. The criteria for exclusion were: serum-cholesterol > 6.4 mmol/litre; serum-triglyceride >2.0 mmol/litre.

Design of the study

The study was performed over a period of 18 days. The six test solutions were given to the subjects using a pattern of multiple crossover design. Each of the 14 subjects received four different aqueous sweetener solutions, a sucrose solution as a comparison and water as a control on an empty stomach on a total of six test days. The sweetener and sucrose solutions were adjusted to normal consumption levels and were of similar sweetness. The actual quantities of each sweetener in 330 mls of water were: aspartame, 165 mg; acesulfame-k, 165 mg; cyclamate, 800 mg; saccharin, 75 mg; and sucrose, 33 g. The subjects were asked to drink the test solutions within five minutes after which four millilitre aliquots of blood were drawn at 0, 5, 10, 15, 30, 60 and 120-minute intervals to measure the levels of insulin and glucose in the blood. At the beginning of the study, and after its conclusion on the sixth test day, a venous blood sample was taken to determine the serum-lipids and lipoproteins.

Analytical methods

Plasma insulin was measured by an enzyme-linked immunological method (Enzymuntest Humaninsulin, Boehringer Mannheim). The normal range lies between 3 to 17 µU/ml. The concentration of glucose in the blood was determined with the GOD-PAP-Method (MerckotestR Diagnostica Merck, Darmstadt). The normal range lies between 3.9 to 6.1 mmol/litre. The total cholesterol and HDL-cholesterol was recorded enzymatically (CHOD-PAP-Method, Boehringer Mannheim). The triglyceride concentration was determined by a total enzymatic method after Wahlefeldt (UV-Test, Boehringer Mannheim). The LDL-cholesterol concentration was estimated using the lipid measurements in the plasma after the formula of Friedewald: LDL-C = Ct - TG/2.2 - HDL-C (mmol/litre).

Biometric analysis

The paired t-test and linear regression analysis were applied (SPSS-system) to show significant differences in the plasma insulin and blood glucose data. Statistics were used to determine whether either the insulin concentration or the blood glucose concentration (which depends on insulin levels) varied significantly over time in comparison to the baseline value obtained at time 0. In addition, the various test treatments were analysed to determine whether insulin and blood glucose levels varied significantly according to the intake of various sweeteners or from the sucrose and water controls. Linear regression was used to show whether or not any of the effects on insulin or glucose levels were time-dependent.
Tab. 1: The influence of orally given aqueous solutions of aspartame, acesulfame-K, cyclamate, saccharin and sucrose on the concentration of plasma insulin in comparison to water (n = 14)

<table>
<thead>
<tr>
<th>Test Substance</th>
<th>0 min</th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>9.78±1.68</td>
<td>9.81±2.02</td>
<td>10.09±2.64</td>
<td>9.95±2.30</td>
<td>9.52±2.24</td>
<td>11.10±7.13</td>
<td>11.12±5.43</td>
</tr>
<tr>
<td>Sucrose</td>
<td>9.93±2.50^b</td>
<td>14.26±4.62^a</td>
<td>21.06±4.04^a</td>
<td>28.04±7.94^a</td>
<td>32.93±7.99^a</td>
<td>16.77±5.96^a</td>
<td>11.46±3.88^c</td>
</tr>
<tr>
<td>Aspartame</td>
<td>10.57±2.94^c</td>
<td>11.68±4.19^c</td>
<td>11.74±3.67^c,d</td>
<td>10.77±3.35^c,d</td>
<td>9.63±2.20^d</td>
<td>9.80±2.06^c,d</td>
<td>9.40±1.59^c,d</td>
</tr>
<tr>
<td>Acesulfame K</td>
<td>10.00±2.75^c</td>
<td>9.52±2.60^c,d</td>
<td>10.24±2.68^c,a</td>
<td>9.78±2.52^c,a</td>
<td>9.65±2.35^c,a</td>
<td>9.55±3.32^c,a</td>
<td>9.71±3.17^c</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>10.28±2.54^c</td>
<td>10.85±3.43^c,d</td>
<td>10.86±4.01^c,a</td>
<td>11.15±3.38^c,a</td>
<td>10.03±3.52^c,d</td>
<td>10.75±3.29^c,a</td>
<td>11.54±3.88^c</td>
</tr>
<tr>
<td>Saccharin</td>
<td>10.91±2.54^c</td>
<td>11.50±3.76^a</td>
<td>11.45±4.41^c,d</td>
<td>11.26±2.37^c,d</td>
<td>10.44±2.00^c,d</td>
<td>10.63±2.47^c,d</td>
<td>10.71±1.73^c</td>
</tr>
</tbody>
</table>

Figures in mean ± SD
P: Probability of error in the paired t-test (two-tailed)

a. Sucrose vs. water: statistically significant P <0.01
b. Sucrose vs. water: statistically not significant P >0.05
c. Sweeteners vs. water: statistically not significant P >0.05
d. Sweeteners vs. sucrose: statistically significant P <0.01

Results

The concentrations of plasma insulin and blood glucose did not vary significantly from the normal range at any measurement time following ingestion of either the water control or any of the four different sweetener solutions. Consequently, there were no differences on the levels of plasma insulin or blood glucose between the water control and any of the four sweeteners tested (Tables 1, 2). However, a solution of sucrose causes a significant rise in plasma insulin and blood glucose values in comparison to sweetener and water. As expected, these values exceed the normal range in the time period between 10 and 30 minutes following ingestion (Tables 1, 2).

The influence of sweeteners on insulin

• The influence of sweeteners on the time dependent secretion of insulin
No statistically significant changes in the concentration of plasma insulin were found at any time following the ingestion of either the water control or any of the aqueous solutions of sweeteners. However, ingestion of a solution of sucrose stimulated the secretion of insulin to levels which differ significantly from those found after the intake of a solution of any of the sweeteners (P<0.001) (Table 1).

• The influence of sweeteners on the maximum secretion of insulin
No statistically significant differences in the maximum concentration of plasma insulin were found following the ingestion of either the water control or any of the aqueous solutions of sweeteners. In all cases, the level of plasma insulin remained in the normal range. However, ingestion of a solution of sucrose produced a maximum concentration of plasma insulin significantly different from the concentration produced by the intake of a solution of any of the sweeteners (P<0.001).
Ingestion of solutions of sweeteners caused no physiologically important changes in the level of blood glucose in contrast to the sucrose control (Table 2). Ten minutes after ingestion of aqueous solutions of saccharin, the blood glucose level was statistically significantly lower than for the water control. However, this observation has no physiological relevance since the blood glucose level was within the normal range and not less than its value at the start of the experiment (time 0) (Table 2). Similarly, table 2 shows that, 60 minutes after ingestion of aqueous solution of aspartame, the blood glucose level was also statistically significantly lower than for the water control. This difference results from a reaction which is independent of insulin. The most important consideration, however, is that the blood glucose levels observed after ingestion of solutions of saccharin and aspartame remain within the normal range and are, therefore, not physiologically meaningful.

**Serum-lipids and lipoproteins**

Significant decreases were observed in comparison to the initial values for both total cholesterol and serum-LDL-cholesterol. A slight increase in serum-HDL-cholesterol and a slight decrease in serum-triglycerides was observed (Table 3).
Tab. 3: Serum-lipids and lipoproteins at the beginning and end of the study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Beginning</th>
<th>End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum-Cholesterol (mmol/l)</td>
<td>5.53±0.97</td>
<td>4.58±0.55a</td>
</tr>
<tr>
<td>Serum-HDL-Cholesterol (mmol/l)</td>
<td>1.41±0.27</td>
<td>1.46±0.31</td>
</tr>
<tr>
<td>Serum-LDL-Cholesterol (mmol/l)</td>
<td>3.52±1.01</td>
<td>2.77±0.63b</td>
</tr>
<tr>
<td>Serum-Tryglyceride (mmol/l)</td>
<td>0.87±0.52</td>
<td>0.77±0.47</td>
</tr>
</tbody>
</table>

Figures in mean ±SD
P: Probability of error in paired t-test (two-tailed)
a. Statistically significant P <0.01
b. Statistically significant P <0.01

Discussion

The results of this study show that ingestion of the low calorie sweeteners aspartame, acesulfame-k, cyclamate and saccharin, which are different in their chemical structure, cause no changes in the level of plasma insulin during the two hour period of observation. Blood glucose levels, which are regulated by insulin, are also not affected in a time-dependent way. No values measured after the ingestion of sweetener solutions departed from the normal range, nor were they significantly different from the values obtained following ingestion of water, except for two physiologically irrelevant values (Tables 1, 2).

As expected, ingestion of sucrose caused significant changes in the blood glucose level for periods of up to 30 minutes when compared to the levels measured following ingestion of any of the low calorie sweeteners or the water control. The absence of time-dependent effects on the secretion of insulin and the level of blood glucose was confirmed by linear regression analysis (Tables 4, 5).

Tab. 4: Time-dependent effects of sweeteners on plasma insulin determined by linear regression analysis (n = 14)
Plasma insulin (t) = b x t + a

<table>
<thead>
<tr>
<th>Test Substance</th>
<th>Regression Coefficient (b)</th>
<th>Section of Axis (a)</th>
<th>Standard Deviation (Sxy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0.0132</td>
<td>9.7574</td>
<td>0.3879</td>
</tr>
<tr>
<td>Sucrose</td>
<td>-0.0498</td>
<td>20.1919</td>
<td>0.1776</td>
</tr>
<tr>
<td>Aspartame</td>
<td>-0.0164</td>
<td>11.0754</td>
<td>0.7066</td>
</tr>
<tr>
<td>Acesulfame-K</td>
<td>-0.0020</td>
<td>9.8517</td>
<td>0.2685</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>0.0072</td>
<td>10.4433</td>
<td>0.4527</td>
</tr>
<tr>
<td>Saccharin</td>
<td>-0.0054</td>
<td>11.1707</td>
<td>0.3848</td>
</tr>
</tbody>
</table>

Tab. 5: Time-dependent effects of sweeteners on blood glucose determined by linear regression analysis (n = 14)
Glucose in blood (t) = b x t + a

<table>
<thead>
<tr>
<th>Test Substance</th>
<th>Regression Coefficient (b)</th>
<th>Section of Axis (a)</th>
<th>Standard Deviation (Sxy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0.00002</td>
<td>4.9092</td>
<td>0.0838</td>
</tr>
<tr>
<td>Sucrose</td>
<td>-0.0135</td>
<td>6.2947</td>
<td>1.0935</td>
</tr>
<tr>
<td>Aspartame</td>
<td>0.0016</td>
<td>4.5551</td>
<td>0.2091</td>
</tr>
<tr>
<td>Acesulfame-K</td>
<td>-0.0001</td>
<td>4.8479</td>
<td>0.1262</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>-0.0002</td>
<td>4.8342</td>
<td>0.0678</td>
</tr>
<tr>
<td>Saccharin</td>
<td>0.0015</td>
<td>4.6714</td>
<td>0.1099</td>
</tr>
</tbody>
</table>
It is clear that none of the low calorie sweeteners tested in this study caused a hypoglycaemic effect (lowered blood sugar).

With the ingestion of similarly sweet aqueous solutions of sweeteners and sucrose, the possible influences of other substances were excluded, which, the literature suggests, might trigger a cephalic secretion of insulin analogous to the physiological secretion caused by sucrose [9]. In the present study, none of the tested sweeteners caused a measurable increase in the plasma insulin level which suggests that no cephalic secretion of insulin occurred.

Similarly, none of the tested low calorie sweeteners had an effect on the blood glucose level which regulates feelings of hunger. Under the conditions of this study, no data were found to suggest that low calorie sweeteners cause physiologically triggered feelings of hunger.

References:


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