Comparison of Secretin Response to Oral Intraludodenal or Intravenous Glucose Administration*

D.J. Chisholm**, E.W. Kraegen, J.D. Young † and L. Lazarus
Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney, 2010, Australia

Summary

Previous studies of the pancreatic exocrine response to intraludodenal glucose administration have not demonstrated the release of secretin; consequently, the importance of secretin in the enteric insulin release mechanism has been questioned.

In this study, serum levels of secretin were estimated by radioimmunoassay in three normal subjects after oral, intravenous or intraludodenal administration of glucose (1 gm per Kg). No secretin response was recorded during the intravenous study but similar peak levels (12 to 18 ng per ml) were observed with the oral and intraludodenal routes of administration. The initial response was rapid in both instances, but the effect was more prolonged after intraludodenal administration. As secretin is known to potentiate the glycaemic release of insulin, it is postulated that this hormone is a major factor in the augmented insulin response observed during both oral and intraludodenal studies.

Horm. Metab. Res. 3: 180-183 (1971)

Key Words: Secretin Release – Insulin Release – Glucose Administration – Radioimmunoassay

Introduction

It has been shown that the oral or intestinal administration of glucose stimulates a greater release of insulin than the intravenous route (McIntyre, Holdsworth and Turner 1965, Elrick, Stimmier, Hlad Jr. and Arai 1964, Dupré and Beck 1966, Perley and Kipnis 1967) and that secretin plays a major role in augmenting the insulin release after oral glucose (Chisholm, Young and Lazarus 1969, Kraegen, Chisholm, Young and Lazarus 1970).

We have here examined whether secretin also plays an operative role in insulin release after intestinal administration of glucose. There is some doubt that this is so as a recent study failed to show a significant increase in pancreatic exocrine function after intestinal delivery of a glucose load (Sum and Preshaw 1967).

The conclusion reached by Sum and Preshaw was that secretin could not be a factor in the augmented insulin release in this situation. This problem has been re-examined using radioimmunoassays for secretin

(Young, Lazarus, Chisholm and Atkinson 1968) and insulin (Young and Kraegen 1968) to carry out a comparative evaluation of the responses of these hormones to equivalent total loads of glucose given by either oral, intraludodenal or intravenous administration in normal subjects.

Materials and Methods

A glucose load of 1 gm per kg was administered by either oral, intraludodenal or intravenous routes to three normal, non-obese, informed subjects aged 19 to 21. Each study was conducted in the morning after a minimum eight-hour fast. The oral load was dissolv ed in 120 ml water and swallowed rapidly; the intraludodenal and intravenous loads were administered as a constant infusion of 14 ml per minute over 60 minutes, the former via a No. 12 F. G. Ryles tube located fluoroscopically in the duodenum (the glucose concentration of the infusion was adjusted to give a total load of 1 gm per kg body weight and was approximately 8 gm per 100 ml). Blood samples were obtained from an indwelling polythene catheter inserted in an antecubital vein at least 30 minutes prior to the commencement of the study and the intravenous infusion was administered via a similar catheter in the contralateral forearm.

Plasma glucose levels were measured by the autoanalyser modification of the Hoffmann ferricyanide technique (Hoffmann 1937) and serum insulin (Young and Kraegen 1968) and secretin (Young et al. 1968, Chisholm, Young and Lazarus 1969) levels by radioimmunoassay.

All insulin and secretin estimations were performed in the same assay batches.

Results

The figure demonstrates the serum secretin response of the three subjects to oral and intraludodenal glucose administration. In both situations there was an early elevation of serum secretin of approximately equal magnitude. The elevation, however, is more prolonged in all subjects after intraludodenal glucose. This is evident in the integrated secretin response (area under serum secretin curve over time range 0 to 120 minutes) which is approximately twice as great after intraludodenal as after oral glucose (Table). No recordable le-
Table 1. Peak levels (max.), elevation above basal levels ($\Delta$) and integrated responses (i.e. incremental area under the curve from 0 to 120 min.) of plasma glucose, serum secretin and serum insulin after different routes of glucose administration.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Serum secretin* (mg/ml)</th>
<th>Integrated secretin response (ng/min/ml)</th>
<th>Plasma glucose (mg/100 ml)</th>
<th>Serum insulin (uL/mL)</th>
<th>Integrated insulin response (uL/min/ml)</th>
<th>Ratio $\Delta I/\Delta G$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P.C.</td>
<td>13</td>
<td>180</td>
<td>181</td>
<td>87</td>
<td>61</td>
<td>54</td>
</tr>
<tr>
<td>M.W.</td>
<td>13</td>
<td>170</td>
<td>116</td>
<td>25</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>route</td>
<td>C.J.</td>
<td>12</td>
<td>170</td>
<td>118</td>
<td>29</td>
<td>45</td>
</tr>
<tr>
<td>Mean</td>
<td>13</td>
<td>170</td>
<td>138</td>
<td>47</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>Intra-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>duodenal</td>
<td>P.C.</td>
<td>13</td>
<td>350</td>
<td>130</td>
<td>48</td>
<td>81</td>
</tr>
<tr>
<td>M.W.</td>
<td>12</td>
<td>280</td>
<td>237</td>
<td>157</td>
<td>73</td>
<td>67</td>
</tr>
<tr>
<td>route</td>
<td>C.J.</td>
<td>18</td>
<td>410</td>
<td>108</td>
<td>24</td>
<td>67</td>
</tr>
<tr>
<td>Mean</td>
<td>14</td>
<td>350</td>
<td>158</td>
<td>76</td>
<td>74</td>
<td>66</td>
</tr>
<tr>
<td>Intra-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>venous</td>
<td>P.C.</td>
<td>0</td>
<td>0</td>
<td>244</td>
<td>155</td>
<td>26</td>
</tr>
<tr>
<td>M.W.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>327</td>
<td>237</td>
<td>44</td>
</tr>
<tr>
<td>route</td>
<td>C.J.</td>
<td>0</td>
<td>0</td>
<td>215</td>
<td>128</td>
<td>44</td>
</tr>
<tr>
<td>Mean</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>262</td>
<td>173</td>
<td>38</td>
</tr>
</tbody>
</table>

* As fasting levels were unrecordable in 17 of 18 estimations, S max is equivalent to $\Delta S$. 
The maximum serum IRI levels and the integrated insulin response recorded after intraduodenal glucose exceeds the respective levels recorded after oral glucose in all subjects (Table). The insulin response to both alimentary studies exceeded the response to the intravenous infusion, and the ratios of the maximum increment of serum insulin to the maximum increment of blood glucose were considerably greater.

The highest plasma glucose levels were recorded in the intravenous studies. Two of the three subjects showed lower maximum glucose levels during the intraduodenal study than the corresponding oral study, although the mean maximum glucose level was higher after intraduodenal administration. Urinary glucose loss varied from 2.0 to 5.3 gm in the intravenous studies, but was noted in only one (2 gm loss) of the alimentary studies.

Discussion

Secretin is a dominant factor in the release of insulin after oral glucose (Chisholm, Young and Lazarus 1969, Kraegen et al. 1970) but previous studies have suggested that there is no release of secretin after intestinal glucose administration (Sum and Preshaw 1967, Wang and Grossman 1951). The present study has used an immunoassay for secretin to determine serum levels of this hormone. Using the intraduodenal route, it was found that an early secretin response is recorded which is similar in magnitude to but more prolonged than the response to oral glucose (Figure).

The rapidity of the response to the intraduodenal load and the rapid fall-off despite continued stimulus is worthy of note. Gastrin, which has been implicated as the initial trigger to secretin release after the oral load (Chisholm, Young and Lazarus 1969), would not be present in this situation. Studies (Kraegen 1969) using a radioimmunoassay for gastrin have shown no elevation of serum levels after intraduodenal glucose administration. Thus, it is suggested that the direct delivery of glucose into the duodenum itself causes a rapid release of secretin. The subsequent rapid decline in serum levels despite continuing stimulus might be due to the exhaustion of readily available stores of hormone with an insufficient stimulus to cause further rapid synthesis. A similar phenomenon was noted with intravenous infusion of pentagastrin (Chisholm, Young and Lazarus 1969). This observation might also be explained by feedback inhibition either by insulin (Chisholm, Lazarus, Young and Kraegen 1970) or by pancreatic exocrine secretion. The reason for the disparity between this report and previous studies (Sum and Preshaw 1967, Wang and Grossman 1951) is not apparent, but there could be several explanations apart from the possibility of a species difference in the latter of these studies. First, a difference in threshold for exocrine and endocrine effects of secretin might permit a rise in serum levels detectable by immunoassay and sufficient to potentiate insulin release but not reaching the threshold for a significant exocrine response. This hypothesis is supported by the evidence that very small amounts (10 U) of secretin have a powerful potentiating effect on insulin release (Kraegen et al. 1970). Second, it is possible that factors other than secretin may have a secretin-like exocrine effect on the pancreas (Dupré 1970) so that the activation of such a mechanism by acid rather than glucose could have accentuated the difference in exocrine response to these two stimuli independently of their effect on secretin release.

Third, it is acknowledged that measurement of pancreatic exocrine secretion in man may be subject to error. Although the three subjects of Sum and Preshaw (1967) did not show a bicarbonate response, the only subject on whom volume output was recorded did show some increase during glucose administration (Boekus, Lopsniak and Tachdjian 1965), and it seems quite possible that a small secretin response might be missed in an animal preparation where a
background infusion of secretin is used (Wang and Grossman 1951). On the other hand, as with all radioimunoassay measurements, there cannot be absolute certainty as to the identity and biological activity of the immunologic material. In this case, however, previous studies have shown an acceptable response to known stimuli (Chisholm, Young and Lazarus 1969) and absence of immunological cross reactivity with the hormones most closely related structurally, i.e. glucagon (Young et al. 1968) and "gut glucagon". Recent testing of a preparation of "gut glucagon" showed no cross-reactivity in the secretin assay up to a concentration of 500 ng/ml. This evidence is strongly in favour of the specificity of the assay.

Although it is not possible to make definite conclusions about the relationship of secretin to the insulin

* Kindly supplied by Dr. Lise Heding, Novo Research Institute.

References


Requests for reprints should be addressed to: Dr. E.W. Kraegen, Garvan Institute of Medical Research, St. Vincent's Hospital, Darlinghurst, N.S.W. 2010 (Australia)