Glucoregulatory disorders in school refusal students

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Summary

OBJECTIVES Our previous studies demonstrated autonomic nervous system disorders and cerebral blood hypoperfusion in school refusal students with underlying emotional distress due to fear or anxiety associated with school attendance. Because severe stress is known to affect glucoregulatory metabolism, this study used the oral glucose tolerance test (OGTT) to measure glucose metabolism in school refusal students.

DESIGN A three-hour OGTT was performed. In preparation for the test, students fasted overnight. After a fasting blood sample was drawn, students were given solutions containing a predetermined amount of glucose based on their body weight (1.75 g/kg to a maximum 75 g). After glucose ingestion, blood samples were drawn at 30, 60, 90, 120, 150, and 180 min to measure blood glucose (BG), immunoreactive insulin (IRI), pancreatic glucagon (IRG) and growth hormone (GH) levels. BG levels, IRI response, cumulative BG (ΣBG), cumulative IRI (ΣIRI), insulin/glucose ratio (∆IRI/∆BG), and insulinogenic index (ΣIRI/ΣBG) were then compared to previously reported normal control data. As an index of emotional difficulties, the self-rating depressive scale (SDS) was carried out.

RESULTS BG levels at all OGTT time intervals and ΣBG were significantly higher in school refusal students than the normal control data (ΣBG: 39.5 ± 4.4 vs 33.3 ± 3.4 mmol/l, P < 0.001). Although the insulin response was abnormally low relative to the prevailing hyperglycaemia (ΣIRI/ΣBG: subjects vs control = 232 ± 129 vs 375 ± 271, P < 0.01), normal beta cell secretory ability was speculated (ΣIRI: subjects vs controls = 2805 ± 1274 vs 2523 ± 1219 pmol/l). This suggests a relative suppression of insulin secretion. A paradoxical increase of GH was observed in 19 students after glucose ingestion.

CONCLUSIONS Glucoregulatory disorders observed in school refusal students may be caused by emotional distress. Multiple factors including autonomic nervous system disorders, derangement of neuropeptides in the hypothalamus, and hormonal imbalances may also affect glucoregulatory metabolism, predisposing these students to hyperglycaemia. We speculate that the glucoregulatory system compensates for decreased blood flow to the brain by increasing blood glucose concentrations, thereby providing sufficient glucose as the primary energy source used during normal brain metabolism.

Introduction

School refusal students often suffer emotional distress due to fear or anxiety associated with school attendance (Last & Strauss, 1990). Many such students we encountered have exhibited various psychological and physical ailments including poor concentration, memory disturbance, generalized fatigue, headache, vomiting, sweating, myalgia, sleep disturbance, and abdominal discomfort. The physical symptoms can be attributable in part to autonomic nervous system disorders. We recently demonstrated depressive states and numerous autonomic nervous system disorders in Japanese school refusal students (Tomoda et al., 1994a, 1994b; Yoshikawa et al., 1995). Furthermore, our most recent study revealed cerebral blood hypoperfusion in many of these students (Tomoda et al., 1995). These findings suggest that the physiological homeostasis of these students may be seriously impaired by severe emotional distress.

Because emotionally stressful events have been shown to result in hyperglycaemia in diabetic patients (Lustman, 1981),...
and the relationship between stress and impaired glucose regulation is thought of as unidirectional (Shamoon et al., 1981; Giacca et al., 1991), it was hypothesized that school refusal students, who are associated with emotional stress, would have a carbohydrate metabolism impairment. To find out, this study used the oral glucose tolerance test (OGTT) to measure their glucose metabolism.

**Subjects and Methods**

**Subjects**

Eighty-one school refusal students (40 males and 41 females), 11–19 years of age (14.8 ± 2.1), were studied. Their school refusal periods ranged from one month to eight years. All students met the following criteria: (1) their major complaint was generalized fatigue, memory disturbance, poor concentration, sleep disturbance, and/or physical complaints including headache, vomiting, sweating, myalgia, and abdominal discomfort; (2) they felt they could not attend school regularly; (3) no organic pathology that could account for the symptoms was detected using appropriate clinical and laboratory investigations or appeared in a medical history taken by a paediatrician. All students were within −15 to +20 % (−0.04 ± 8.6) of their ideal body weight. The students had no personal or family history of diabetes mellitus or liver disease. They were informed of the nature, purpose and possible risks of the study and obtained personal and parental consent.

**Study design**

As an index of emotional difficulties, the self-rating depressive scale (SDS) was carried out (Kovacs, 1981). OGTT was performed in the morning after the students had fasted overnight. On the morning of the study, an indwelling catheter was inserted in an antecubital vein. After a fasting blood sample was drawn, a 1.75 g/kg oral dose of glucose (maximum 75 g) was administered to each student. Blood samples were then drawn at 30, 60, 90, 120, 150, and 180 min following glucose ingestion. All indices were calculated using the same methods as those used for the previously reported normal control data (Seltzer et al., 1967; Matsuura et al., 1984). SBG and SIRI were the cumulative values of fasting BG and IRI levels and the levels measured at 30, 60, 90, 120, and 180 min after oral glucose ingestion. The insulin/glucose ratio (ΔIRI/ΔBG) was calculated by dividing the change in insulin level from the fasting level to 30 min after oral glucose ingestion by the corresponding change in BG level. The insulinogenic index (ΔIRI/ΔBG) was calculated by dividing the area circumscribed by the insulin curve at the fasting level and at 30, 60, 90, 120, and 180 min after oral glucose ingestion (i.e. increase above fasting level) by the corresponding area circumscribed by the glucose tolerance curve.

Data are expressed as mean ± SD. Statistical analysis consisted of an unpaired Student’s t-test and Welch’s t-test (Overall et al., 1995). All results were considered significant at *P* < 0.05.

**Results**

**Self-rating depressive scale (SDS) score**

We could not obtain the consent of all of the school refusal students to answer the SDS questionnaire. However, 52 out of 81 students completed it. The average SDS score was 51.3 ± 9.4 with 90% of the students showing a predisposition for depression (40 points or more).

**Characteristics of glucose response to the OGTT**

BG levels in the school refusal students were significantly higher than the normal control data at all time intervals following oral glucose ingestion (*P* < 0.01) (Table 1). However, the individual BG values at each time interval varied widely, ranging from a maximum of 11.6 mmol/l at 60 min to a minimum of 3.1 mmol/l at 90 min after oral glucose ingestion. The individual glucose tolerance curves showed various

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patterns: monophase hyperglycaemic, delayed hyperglycaemic, and oxyhyperglycaemic-like patterns. Only 12 of the 81 students (15%) showed a normal glucose tolerance curve.

**Insulin response to the OGTT**

Plasma insulin concentration of the school refusal students did not vary significantly from the normal control data at any time interval following oral glucose ingestion except at the fasting level (Table 1). Individually, however, each student’s insulin level varied widely when compared with the corresponding BG level, and in some students insulin level did not correlate with BG level.

**Comparison of indices (Table 2)**

Compared to the normal control data, ΣBG of the school refusal students was significantly elevated (subjects vs controls = 39.5 ± 4.4 vs 33.3 ± 3.4 mmol/l, \( P < 0.001 \)). However, ΣIRI was not significantly different (subjects vs controls = 2805 ± 1274 vs 2523 ± 1219 pmol/l) (Fig. 1). The insulin/glucose ratio (ΣIRI/ΣBG), initial insulin response 30 min after oral glucose ingestion, was not statistically different from that

<table>
<thead>
<tr>
<th>time (min)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG (mmol/l) subjects</td>
<td>4.78 ± 0.46</td>
<td>8.00 ± 1.27</td>
<td>7.61 ± 1.54</td>
<td>6.78 ± 1.33</td>
<td>6.67 ± 1.16</td>
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<td>4.93 ± 0.43</td>
<td>6.50 ± 1.48</td>
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<td>5.56 ± 0.86</td>
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<td>( P &lt; 0.001 )</td>
<td>ND</td>
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</table>

| IRI (pmol/l) subjects | 79 ± 29 | 627 ± 396 | 594 ± 408 | 504 ± 311 | 534 ± 362 | 408 ± 290 | 420 ± 333 |
| controls | 108 ± 76 | 614 ± 327 | 519 ± 357 | 508 ± 361 | 474 ± 272 | ND | 301 ± 272 |
| significance \( ^a \) | \( P < 0.05 \) | ns | ns | ns | ns | ns | ns |

Values are mean ± SD. \( ^a \) Significance of the difference between school refusal subjects and normal control; values greater than \( P = 0.05 \) are not significant. ND: not described. ns: not significant.

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**Table 1** Comparison of BG and IRI between school refusal subjects and normal controls

<table>
<thead>
<tr>
<th>time (min)</th>
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**Table 2** Comparison of indices between school refusal subjects and normal controls

<table>
<thead>
<tr>
<th>indices</th>
<th>ΣBG (mmol/l)</th>
<th>ΣIRI (pmol/l)</th>
<th>ΔIRI/ΔBG</th>
<th>ΣIRI/ΣBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>subjects</td>
<td>39.5 ± 4.4</td>
<td>2805 ± 1274</td>
<td>194 ± 181</td>
<td>232 ± 129</td>
</tr>
<tr>
<td>controls</td>
<td>33.3 ± 3.4</td>
<td>2523 ± 1219</td>
<td>254 ± 129</td>
<td>375 ± 271</td>
</tr>
<tr>
<td>significance ( ^a )</td>
<td>( P &lt; 0.001 )</td>
<td>ns</td>
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</tr>
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Values are mean ± SD. \( ^a \) Significance of the difference between school refusal students and normal controls. Values greater than \( P = 0.05 \) are not significant. ns: not significant.
of the normal control data (subjects vs controls = 194 ± 181 vs 245 ± 129). In eight subjects, however, the ratio was below 65, which level is seen in patients with insulin dependent diabetes mellitus.

No significant correlation was detected between the SDS score or school refusal period and indices of the OGTT data.

**IRG and GH**

Plasma IRG concentrations, measured simultaneously with BG, decreased proportionately in relation to the increase in BG levels. This appears to be normal response (data not shown) (Nishino et al., 1981).

Although serum GH levels should be suppressed during the first 120 min of the OGTT (Hunter et al., 1968; Yalow et al., 1969), values above 10 mU/l were observed in 19 students at 30–120 min after oral glucose ingestion (Fig. 3).
postprandial carbohydrate metabolism. Some students were similar to patients with oxyhyperglycaemia caused by dumping syndrome, and their complaints of fatigue, sweating, dizziness, nausea, palpitation, and abdominal discomfort might be due in part to these glucoregulatory disorders (Berlin et al., 1994).

We must also consider the importance of neuropeptides and neurotransmitters in the hypothalamus, which is believed to be the relaying station for the peripheral metabolism of carbohydrates (Shimazu et al., 1966; Uemura et al., 1989; Hommura et al., 1992; Ozawa et al., 1993). It is generally accepted that physical and psychological stress can have profound neuroendocrine effects, and that nearly all such effects may cause hormonal and metabolic imbalance, thereby upsetting glucose homeostasis (Sasaki et al., 1988). Corticotropin-releasing hormone (CRH), a hypothalamus peptide, is believed to be the central component of the stress system. The disturbance of the circadian rhythm of cortisol and beta-endorphin, recognized in our recent study in a school refusal student, is thought to reflect CRH derangement in the hypothalamus (Tomoda et al., 1994ab).

Although we did not have age-matched normal control data for glucagon levels, plasma IRG concentrations decreased in a normal fashion following oral glucose ingestion (Nishino et al., 1981). This may indicate that the hyperglycaemic predisposition observed in this study is independent of glucagon (Rizza et al., 1979b, 1980). GH, known as a counter-regulatory hormone, increased paradoxically in 23% of the students during the OGTT and may contribute to hyperglycaemia in such cases.

Even with the predisposition for hyperglycaemia in these students, IRI at any time interval during the OGTT and SIRI were not significantly different from the normal control data. However, the insulinogenic index (SIRI/SBG) of the students was significantly lower than the control data, indicating that circulating insulin levels were inappropriately low relative to the prevailing hyperglycaemia, which implies a relative suppression of insulin secretion (Porte et al., 1966; Iversen, 1973; Rizza et al., 1979a; Samols & Weir, 1979).

The insulin/glucose ratio (ΔIRI/ΔBG), representing the initial insulin secretory response to BG change after oral glucose ingestion, was not statistically different between a school refusal students and the normal control data. It was surprising, however, that in 8 of the 81 students the ratio was below 65, which level is seen in patients with insulin dependent diabetes mellitus. In these cases, we hypothesize that such mechanism inhibits insulin secretion in the early phase of OGTT.

Although a complete characterization of the hormonal and metabolic responses to stress is difficult because the interaction of the related substances is complex, the tendency toward higher BG levels appears to be triggered by emotional distress or depressive state in school refusal students. We recently examined cerebral blood flow in 55 school refusal students using single-photon emission computed tomography and found that their blood flow in the frontal, temporal, and occipital lobes was lower than that in healthy controls (Tomoda et al., 1995). Based on this evidence, we speculate that the glucoregulatory system compensates for decreased blood flow to the brain by increasing glucose concentrations, thereby providing sufficient glucose for normal brain metabolism.

References


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