Effects of glucose load and/or arginine on insulin and growth hormone secretion in hyperprolactinemia and obesity

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In hyperprolactinemic patients an exaggerated glucose-induced insulin secretion has been reported, but these results have not been confirmed by other researchers. On the other hand, there are few data concerning somatotrope secretion in this condition. In order to clarify these points, in seven normal weight hyperprolactinemic female patients (HP: age 18–46 years, body mass index = 21.8 ± 0.6 kg/m², basal prolactin = 91.7 ± 16.5 µg/l) we studied the effects of glucose load (100 g orally) and/or arginine (0.5 g/kg infused over 30 min) on insulin glucose and growth hormone (GH) levels. These results were compared with those obtained in seven patients with simple obesity (OB: age 23–48 years, body mass index = 38.3 ± 2.6 kg/m²) in whom exaggerated insulin and low GH secretion are well known. Seven normal women (NS: age 26–32 years, body mass index = 20.6 ± 1.9 kg/m²) were studied as controls. The insulin response to glucose in HP (area under curve = 11460.8 ± 1407.5 mU·min·m⁻¹) was not significantly different from NS (7743.7 ± 882.9 mU·min·m⁻¹) and OB (14504.8 ± 1659.9 mU·min·m⁻¹). The arginine-induced insulin release in HP and OB was similar (4219.4 ± 631.7 and 4107.3 ± 643.2 mU·min·m⁻¹, respectively), both being higher (p < 0.02) than in NS (2178.1 ± 290.9 mU·min·m⁻¹). Glucose and arginine had an additive effect on insulin release in HP and NS (19769.1 ± 3249.6 and 10996.6 ± 1201.0 mU·min·m⁻¹, respectively) and a synergistic effect in OB (28117.3 ± 5224.7 mU·min·m⁻¹). In HP the insulin response to the combined administration of glucose and arginine was not significantly different from the one in OB, and both were higher (p < 0.05) than in NS. The increase in glucose levels after glucose administered on its own or combined with arginine was higher (p < 0.02) and longer lasting in OB than in NS and HP. After arginine in OB, the glucose levels did not show the late decrease under baseline values observed in HP and NS. Glucose inhibited GH secretion both in HP and NS (p < 0.05), while arginine stimulated it in all groups, although the GH response in HP and NS was higher (p < 0.03) than in OB. The arginine-induced GH secretion was inhibited by glucose in HP and NS but not in OB. These results demonstrate that both in hyperprolactinemic patients and in obesity there is a clear increase in insulin secretion. The insulin hyperresponsiveness in hyperprolactinemia is more clearly demonstrated by combined stimulation with glucose and arginine. In spite of similar insulin hypersecretion in hyperprolactinemic and obese patients, GH secretion is reduced only in the latter; with these data the hypothesis that somatotrope insufficiency in obesity is due to hyperinsulinism is unlikely.

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The existence of increased insulin secretion and insulin resistance is well known in obesity (1–4) and is coupled with clear reduction of both basal and stimulated somatotrope secretion (5, 6). An increase in glucose-induced insulin secretion in hyperprolactinemic patients has also been reported by some authors (7–11) but not by others (12). Interestingly, recent data in animals and in men suggest that prolactin plays a major role in β-cell trophism, as well as on insulin synthesis and secretion (13–15). On the other hand, there are few data concerning somatotrope secretion in hyperprolactinemia (16).

Glucose and amino acids are well-known insulin segretagogues, both in animals and in men (17, 18). In man a synergistic effect of arginine and glucose upon insulin secretion has also been shown (19–21), and combined administration of these two stimuli has already been studied in an attempt to probe β-cell secretory capacity in diabetic patients (22). On the other hand, in man, glucose and arginine show opposite
influences on GH secretion in normal subjects (23–26). The inhibitory effect of glucose load and the stimulatory effect of arginine seen mediated by stimulation and inhibition, respectively, of hypothalamic somatostatin release (24–26).

Based on the above, in the present study we have aimed at checking that an exaggerated insulin secretion is actually present in hyperprolactinemia. With this goal in mind, we studied insulin and glucose responses to glucose load and/or arginine in normal weight patients with idiopathic hyperprolactinemia and compared these results with those obtained in patients with simple obesity and in normal controls. In order to clarify the influence, if any, of hyperprolactinemia on somatotrope secretion, the GH responses to glucose load and/or arginine were also studied.

Subjects and methods

Seven female patients with idiopathic (N = 3) or tumoral (N = 4, microprolactinomas) hyperprolactinemia (HP: age 18–46 years. BMI = 21.8 ± 0.6 kg/m²) and seven females with abdominal obesity (OB: age 23–52 years, BMI = 38.3 ± 2.6 kg/m²) were studied. Seven normal women (NS: age 26–32 years, BMI = 20.6 ± 1.3 kg/m²) were studied as the control group. All subjects gave their informed consent to take part in the study. The study protocol had been approved by the ethical committee of our department.

All subjects underwent the following tests: glucose (100 g orally at −45 min); arginine (ARG, arginine hydrochloride, 0.5 g/kg infused from 0 to +30 min); glucose + ARG. The tests were performed in random order with an interval of at least 3 days, starting at 09.00 h after an overnight fast and 30 min after a cannula had been placed in an antecubital vein that was kept patent by slow infusion of isotonic saline.

Insulin, glucose, growth hormone (GH) and prolactin (PRL) levels were measured every 15 min from −60 to +120 min. Serum IGF-I levels were also measured basally.

Serum insulin, GH and PRL were measured by immunoradiometric assay (INSIK-5, HGH-CTK IRMA, PRL-CTK IRMA, respectively) provided by Sorin Biomedica (Saluggia, Italy). Inter- and intra-assay coefficients of variation were 6.5–15% and 4.5–13.4% for insulin, 4.9–6.5% and 1.5–2.9% for GH and 3.9–6.8% and 3.3–7.5% for PRL, respectively. Serum IGF-I was measured by a radioimmunoassay provided by Nichols Institute Diagnostic (San Juan Capistrano, CA) after previous acid–ethanol extraction to avoid binding protein interferences. Inter- and intra-assay coefficients of variation were 5.2–8.4% and 2.4–3.0%, respectively. Plasma glucose was measured by the glucose oxidase method (Beckman II glucose analyser, Beckman, Palo Alto, USA).

Results (mean ± SEM) are expressed as absolute values and/or areas under the curve (AUC) calculated from −45 to +120 min. Statistical analysis was performed using non-parametric analysis of variance for multiple groups (Kruskall–Wallis test) and Wilcoxon’s matched pair test where appropriate.

Results

Baseline values

Basal levels of glucose, insulin, IGF-I, GH and PRL are reported in Table 1. In OB and HP, insulin levels were higher (p < 0.02) than in NS. Glucose and IGF-I levels were similar in all groups. In OB, GH levels were lower than in NS and HP (p < 0.01). In HP, PRL levels were higher (p < 0.01) than in NS and OB.

Dynamic tests

Glucose. In OB, the increase in plasma glucose levels observed after glucose administration was higher and longer lasting than in NS (peak: 156.7 ± 15.3 vs 119.5 ± 9.9 mg/dl, AUC: 23 320.2 ± 2052.0 vs 16 361.3 ± 1054 4 mg·min·dl−1; p < 0.02). In HP this increase (145.4 ± 3.8 mg/dl, 17232.1 ± 500.8 mg·min·dl−1) was not statistically different from the one in NS and lower (p < 0.02) than in OB (Fig. 1).

In NS, ARG had a biphasic effect on plasma glucose levels, showing a slight increase at +15 min (peak: 85.7 ± 7.4 vs 73.7 ± 4.9 mg/dl, p < 0.02) and a decrease thereafter ( nadir at +60 min: 59.3 ± 4.0 mg/dl, p < 0.05). In OB, ARG induced a glucose increase (100.6 ± 5.0 vs 86.9 ± 5.5 mg/dl, p < 0.02) overlapping the one in NS; no late decrease of glucose levels was recorded. In HP as in NS, ARG included a biphasic variation of glucose levels, showing a slight increase at +15 min (106.1 ± 4.1 vs 83.3 ± 1.5 mg/dl, p < 0.03) followed by a decrease ( nadir at +60 min: 65.9 ± 3.9 mg/dl, p < 0.03) (Fig. 1). Glucose AUCs after ARG were similar in all groups.

When glucose and ARG were administered together, the plasma glucose responses (NS: 117.7 ± 5.6 mg/dl.

Table 1. Basal glucose, insulin, IGF-I, growth hormone (GH) and prolactin (PRL) levels in normal, obese and hyperprolactinemic subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal subjects</th>
<th>Obese patients</th>
<th>Hyperprolactinemic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>77.4 ± 3.4</td>
<td>86.1 ± 3.6</td>
<td>82.3 ± 1.6</td>
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<tr>
<td>Insulin (mU/l)</td>
<td>6.2 ± 0.8</td>
<td>12.7 ± 2.4</td>
<td>8.8 ± 0.7</td>
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<tr>
<td>IGF-I (µg/l)</td>
<td>130.6 ± 16.8</td>
<td>110.4 ± 16.2</td>
<td>144.3 ± 20.0</td>
</tr>
<tr>
<td>GH (µg/l)</td>
<td>6.2 ± 1.3</td>
<td>0.2 ± 0.1**</td>
<td>3.5 ± 1.9</td>
</tr>
<tr>
<td>PRL (µg/l)</td>
<td>7.8 ± 0.4</td>
<td>4.3 ± 0.7</td>
<td>100.7 ± 19.2**</td>
</tr>
</tbody>
</table>

* Values are mean ± SEM; ** p < 0.01 and * p < 0.02 vs normal subjects.
Glucose $\rightarrow$ NS $\bullet$ OB $\cdot$ HP

Fig. 1. Plasma glucose levels (mg/dl, mean ± sem) after glucose, arginine or glucose plus arginine in normal (NS), obese (OB) and hyperprolactinemic subjects (HP).

14 106.1 ± 421.0 mg·min·dl$^{-1}$; OB: 159.3 ± 14.4 mg·dl$^{-1}$; 20080.8 ± 1904.5 mg·min·dl$^{-1}$; HP: 135.3 ± 6.1 mg·dl$^{-1}$, 15 995.7 ± 874.3 mg·min·dl$^{-1}$) were not significantly different from those observed after glucose alone in all three groups. A late decrease below baseline values was recorded in HP and in NS (68.6 ± 6.7 vs 81.9 ± 1.6 mg/dl, $p < 0.05$) and 59.9 ± 7.0 vs 78.6 ± 2.5 mg/dl, $p < 0.02$, respectively), but not in OB (Fig. 1).

Insulin. In OB the increase in insulin levels observed after glucose administration was higher and longer lasting than in NS (peak: 122.4 ± 22.9 vs 79.3 ± 5.6 mU/l, AUC: 14 504.8 ± 1659.9 vs 7743.7 ± 882.9 mU·min·l$^{-1}$; $p < 0.03$). In HP the insulin response to glucose (97.4 ± 16.0 mU/l, 11 460.8 ± 1407.5 mU·min·l$^{-1}$) was higher than in NS and lower than in OB, but this difference did not attain statistical significance (Fig. 2).

In HP, the ARG-induced insulin response (92.6 ± 17.1 mU/l, 4219.4 ± 631.7 mU·min·l$^{-1}$) was higher (p < 0.02) than the one observed in NS (31.5 ± 5.7 mU/l, 2178.1 ± 290.9 mU·min·l$^{-1}$) and overlapped with the one in OB (63.4 ± 11.1 mU/l, 4107.3 ± 643.2 mU·min·l$^{-1}$) (Fig. 2).

The combined administration of glucose and ARG had an additive effect on insulin secretion in NS (167.2 ± 29.4 mU/l, 10 996.6 ± 1201.0 mU·min·l$^{-1}$, $p < 0.03$ vs glucose or ARG alone) as well as in HP (317.8 ± 77.1 mU/l, 19 769.1 ± 3249.6 mU·min·l$^{-1}$, $p < 0.02$ vs glucose or ARG alone). In OB the combined administration of the two stimuli elicited a synergistic effect on insulin secretion (489.5 ± 93.3 mU/l, 28 117.3 ± 5224.7 mU·min·l$^{-1}$, $p < 0.05$ vs glucose plus ARG). The insulin responses to glucose load plus

Fig. 2. Plasma insulin levels (mU/l, mean ± sem) after glucose, arginine or glucose plus arginine in normal (NS), obese (OB) and hyperprolactinemic subjects (HP).
ARG in OB and HP were similar and remarkably higher (p < 0.02 and p < 0.05, respectively) than in NS. Interestingly, in OB but not in HP and NS the peak insulin response to glucose load was anticipated by ARG co-administration (at +30 vs +75 min) (Fig. 2).

Growth hormone. Table 2 reports GH values observed before and after glucose, ARG and glucose plus ARG administration. In NS and HP, GH levels decreased (p < 0.05) after glucose and increased (p < 0.05) after ARG administration. This latter response was inhibited significantly (p < 0.05) by previous glucose administration in NS and HP. In OB, the GH response to ARG was lower (p < 0.05) than in NS and HP, while glucose failed to decrease it any further.

Prolactin. The PRL levels were not modified by glucose load in any of the groups. Arginine, either alone or in combination with glucose, significantly increased PRL levels in NS and OB, but not in HP. On the other hand, the PRL response to ARG alone or combined with glucose was lower (p < 0.05) in OB than in NS (Table 3).

Side effects. No side effects were observed after administration of glucose and/or arginine in any of the groups.

Discussion

Our present data clearly demonstrate that in normal weight patients with hyperprolactinemia, insulin secretion is exaggerated and similar to the one in obese patients. What is interesting to note is the fact that insulin hyperresponsiveness in hyperprolactinemia is more clearly apparent after combined stimulation with glucose and ARG, which have a well-known synergistic activity on beta cell secretion (19, 20). On the other hand, somatotrope responsiveness to ARG is preserved in hyperprolactinemia, while it is reduced in obesity.

An exaggerated insulin response to oral glucose load has already been reported both in physiological (pregnancy) and pathological (idiopathic and tumoral) hyperprolactinemia (7–11, 27); it was found to be reversed by PRL normalization after pregnancy (9) or during treatment with dopaminergic agonists (8). Insulin hyperresponsiveness to glucose load, however, was not confirmed by other authors (12). In the present study, hyperprolactinemic patients showed a higher insulin response to oral glucose load than in controls but this difference did not attain statistical significance. On the other hand, in hyperprolactinemia the insulin responsiveness was significantly higher than in controls after stimulation with ARG alone and to a greater extent after combined stimulation with ARG and glucose. After glucose load plus ARG we noted that the exaggerated insulin response in hyperprolactinemic patients overlapped with that observed in obese patients. On the whole, our present findings agree with previous data (12) showing that in hyperprolactinemia the insulin hyperresponsiveness is not detected by glucose load alone, but is clearly unmasked by ARG.

To explain the existence of insulin hypersecretion in hyperprolactinemia, there are data in animals and in man showing that PRL has a stimulatory influence on insulin secretion (13, 14). In fact, PRL exerts a trophic

Table 2. Growth hormone levels (μg/l) before and after glucose, arginine and glucose + arginine administration in normal, obese and hyperprolactinemic subjects.*

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal subjects</th>
<th>Obese patients</th>
<th>Hyperprolactinemic patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Glucose</td>
<td>7.0 ± 1.5</td>
<td>0.4 ± 0.1*</td>
<td>0.1 ± 0.0</td>
</tr>
<tr>
<td>Arginine</td>
<td>4.4 ± 1.9</td>
<td>17.6 ± 4.7*</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>Glucose + arginine</td>
<td>7.5 ± 2.7</td>
<td>9.0 ± 1.5†</td>
<td>0.1 ± 0.1</td>
</tr>
</tbody>
</table>

* Values are means ± sem; * p < 0.05 vs before and † p < 0.05 vs normal subjects.

Table 3. Prolactin levels (μg/l) before and after glucose, arginine and glucose + arginine administration in normal, obese and hyperprolactinemic subjects.*

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal subjects</th>
<th>Obese patients</th>
<th>Hyperprolactinemic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Glucose</td>
<td>7.6 ± 0.5</td>
<td>7.2 ± 0.7</td>
<td>4.5 ± 0.8</td>
</tr>
<tr>
<td>Arginine</td>
<td>7.7 ± 0.5</td>
<td>20.6 ± 2.8*</td>
<td>4.4 ± 1.0</td>
</tr>
<tr>
<td>Glucose + arginine</td>
<td>8.6 ± 1.2</td>
<td>24.4 ± 5.0</td>
<td>4.5 ± 0.8</td>
</tr>
</tbody>
</table>

* Values are means ± sem; * p < 0.05 vs before and † p < 0.05 vs normal subjects.
action on pancreatic beta cells and stimulates both insulin synthesis and release (13–15). Interestingly, in the rat, the effect of PRL on insulin synthesis and secretion as well as on beta cell proliferation has been found to be considerably higher than GH (13, 28). Moreover, more recent data indicate that the effects of GH on beta cell tropism and secretion are mediated via lactotrope receptors (29).

In the present study we found that glucose load in obese patients induced an increase in plasma glucose levels that was higher and long lasting than in controls and in hyperprolactinemic patients. Moreover, in contrast to controls and hyperprolactinemic patients, ARG failed to induce a glucose decrease in obesity. This peculiar plasma glucose pattern could be due to the well-known insulin resistance present in obesity (4). The evidence that hyperprolactinemic patients showed an ARG-induced glucose pattern similar to normals suggests that insulin hypersecretion is not due to peripheral insulin resistance (10, 30).

As regards somatotrope secretion, we found that the ARG-induced GH response is preserved in hyperprolactinemia but is reduced in obesity. In obesity, the impairment of both spontaneous and stimulated GH secretion is well known (5, 6). In order to explain this GH insufficiency, it has been hypothesized that hypothalamic and/or metabolic alteration could have a role (31–35). It has been suggested that hyperinsulinemia plays a major role in the various metabolic alterations of obesity (36, 37). Our present data showing that hyperprolactinemic patients have normal GH secretion despite insulin hypersecretion, similar to obese patients, seem to go against the hypothesis that GH insufficiency in obesity is due to exaggerated insulin secretion.

To conclude, we can say that the present data confirm that in patients with hyperprolactinemia PRL secretion is, at least partly, refractory to stimulation (16). Reduced lactotrope responsiveness to stimulation has also been reported in obesity (38, 39). In the present study we agree with these data by finding a trend toward low PRL responsiveness in obese patients.

In conclusion, the results of the present study reinforce the hypothesis that hyperprolactinemia is a condition of insulin hypersecretion and underline the metabolic role of PRL in humans.

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