Distribution volume, metabolic clearance and plasma half disappearance time of exogenous luteinizing hormone releasing hormone in normal women and women with obesity and anorexia nervosa

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Abstract. Synthetic LRH was infused into normal women and women with obesity and anorexia nervosa to determine the distribution volume (DV), metabolic clearance rate (MCR) and half disappearance time (t½) of plasma LRH.

In normal women, the DV of LRH was 12.1 ± 0.9 (mean ± se) l, the MCR was 1478.9 ± 39.8 ml/min (28.5 ± 1.2 ml/min/kg body weight) and the initial t½ was 5.6 ± 0.4 min.

In obese patients the DV (20.6 ± 1.5 l) was significantly higher than that in normal subjects (P < 0.005), but the MCR and t½ were not significantly different from those in normal subjects.

In patients with anorexia nervosa the DV and MCR were 6.5 ± 1.1 l and 621.8 ± 110.5 ml/min (17.9 ± 2.4 ml/min/kg body weight), respectively, which were both significantly lower than those in normal subjects (P < 0.02), while the t½ (7.3 ± 0.1 min) was longer than in normal subjects (P < 0.02).

These data suggest that 1) the abnormal responses of some hormones to provocation tests observed in obese patients and patients with anorexia nervosa should be evaluated in consideration of changes in the DV and metabolic clearance of hormones in these conditions, and 2) in patients with anorexia nervosa changes in MCR and t½ may reflect low metabolism of LRH.

Various endocrine and metabolic abnormalities have been found in obese subjects (Beck et al. 1964; Copinschi et al. 1967) and underweight subjects (Frankel & Jenkins 1975). As we previously reported, the release of some pituitary hormones in response to various stimuli is impaired in obese patients (Chikamori 1976), and elevation of the plasma growth hormone (GH) level and decrease in luteinizing hormone (LH) secretion are noted in many patients with anorexia nervosa (Nishimura et al. 1979). These abnormalities in hormone secretion have been considered as secondary changes due to change in the body weight or dysfunction of the hypothalamo-pituitary axis. However, the plasma concentration of a hormone reflects a balance between the rates of its secretion and metabolism, and thus endocrine function should be evaluated on the basis not only of the plasma concentration but also of metabolic clearance of the hormone released from the endocrine gland.

For investigation of this problem, it is necessary to study changes in the distribution volume (DV) and metabolic clearance rate of hypothalamic or pituitary hormones in patients with obesity and anorexia nervosa. At present few purified pituitary hormones are available for iv injection into humans, but hypothalamic releasing hormone is readily available.

The metabolic clearance of synthetic luteinizing hormone releasing hormone (LRH) in normal subjects has been studied (Miyachi et al. 1973; Keye et al. 1973), but little is known about changes in metabolic clearance of LRH in diseased states (Pimstone et al. 1977). Therefore, we studied the DV, metabolic clearance rate (MCR) and half disap-
pearance time (t½) of synthetic LRH in patients with obesity and anorexia nervosa using a specific radioimmunoassay for LRH which we have developed (Saito et al. 1975).

Materials and Methods

Subjects

Four normal women aged 22–40 years, 5 obese women with no endocrine disease and normal glucose tolerance aged 21–37 years, and 3 women with anorexia nervosa aged 23–28 years were studied. The mean percentage deviations of the body weight of these women from the ideal weights given in Matsuki's table (Matsuki et al. 1971), were −6.8 ± 2.6 for normal subjects, +56.3 ± 9.4 for obese subjects, and −39.0 ± 3.2 for patients with anorexia nervosa. Relevant clinical data of the subjects are summarized in Table 1.

**Table 1.**
Clinical data of the subjects.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Percentage deviation from ideal weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F. S.</td>
<td>F</td>
<td>27</td>
<td>155</td>
<td>48</td>
<td>−9.4</td>
</tr>
<tr>
<td>H. T.</td>
<td>F</td>
<td>22</td>
<td>159</td>
<td>50</td>
<td>−9.6</td>
</tr>
<tr>
<td>K. H.</td>
<td>F</td>
<td>25</td>
<td>162</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>K. C.</td>
<td>F</td>
<td>40</td>
<td>165</td>
<td>53</td>
<td>−8.1</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td></td>
<td>28.5 ± 3.9</td>
<td>159.8 ± 2.1</td>
<td>52.0 ± 1.9</td>
<td>−6.8 ± 2.6</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K. Y.</td>
<td>F</td>
<td>28</td>
<td>155</td>
<td>90</td>
<td>+69.8</td>
</tr>
<tr>
<td>K. H.</td>
<td>F</td>
<td>31</td>
<td>156</td>
<td>94</td>
<td>+74.8</td>
</tr>
<tr>
<td>R. C.</td>
<td>F</td>
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<td>155</td>
<td>68</td>
<td>+28.3</td>
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<tr>
<td>K. S.</td>
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<td>27</td>
<td>165</td>
<td>93</td>
<td>+61.2</td>
</tr>
<tr>
<td>Y. I.</td>
<td>F</td>
<td>21</td>
<td>155</td>
<td>78</td>
<td>+47.2</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td></td>
<td>28.8 ± 2.9</td>
<td>156.8 ± 1.7</td>
<td>84.6 ± 5.6</td>
<td>+56.3 ± 9.4</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. O.</td>
<td>F</td>
<td>27</td>
<td>152</td>
<td>32</td>
<td>−38.8</td>
</tr>
<tr>
<td>F. K.</td>
<td>F</td>
<td>23</td>
<td>167</td>
<td>34</td>
<td>−43.6</td>
</tr>
<tr>
<td>M. S.</td>
<td>F</td>
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<td>161</td>
<td>37</td>
<td>−34.5</td>
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<tr>
<td>Mean ± SE</td>
<td></td>
<td>26.0 ± 1.9</td>
<td>160.0 ± 5.3</td>
<td>34.3 ± 1.8</td>
<td>−39.0 ± 3.2</td>
</tr>
</tbody>
</table>

Infusion of LRH and sample collection

In the early morning after overnight fasting, the subjects were given 200 μg of synthetic LRH (Tanabe Pharmaceutical Co., Osaka, Japan) in 12 ml of physiological saline by infusion into a superficial arm vein over a period of 60 min at a constant rate of 3.33 μg per min using an infusion pump. Blood samples were withdrawn from a contralateral arm vein through an indwelling catheter into test tubes containing ethyl-p-(6-guanidino hexanoyloxy)-benzoate methanesulphonate (Ono Pharmaceutical Co., Osaka, Japan), a proteolytic enzyme inhibitor, to give a final concentration of 1 mM. Samples were taken every 5 min during the infusion period and every 2 min for the next 16 min after cessation of the infusion.

Assay procedure

Plasma was immediately separated in the cold, extracted with 6 volumes of cold methanol and stored frozen until determination of LRH. LRH was measured by radioimmunoassay using specific antiserum against synthetic LRH as described previously (Saito et al. 1975).

Distribution volume (DV), MCR and half disappearance time (t½)

The DV is definable as apparent volume of distribution of LRH in the plasma and tissue, and t½ is its half disappearance time from circulation. The MCR means metabolic clearance rate of LRH, which is identical to the product of DV and disappearance constant. These values
Synthetic LRH infusion (3.33 µg/min)

Fig. 1.
Plasma LRH levels during and after cessation of infusion of synthetic LRH in normal subjects, patients with obesity and anorexia nervosa. LRH was infused at a rate of 3.33 µg/min for 60 min. Points are means ± SE.

were calculated by the method of Tait et al. (1961). MCR (ml/min) was determined when the steady state conditions were reached during constant infusion of LRH from the formula MCR = R/i, where R is the rate of infusion of synthetic LRH (3333 ng/min) and i is the plasma LRH concentration under steady state conditions in ng/ml. The t½ value was calculated by direct extrapolation from the disappearance slope derived from the plasma concentration of LRH plotted logarithmically against the time after stopping LRH infusion. DV was calculated as the MCR of LRH divided by the disappearance constant.

Results

Plasma LRH concentrations during and after LRH infusion
The plasma LRH concentrations during and after LRH infusion in normal subjects, and patients with obesity and anorexia nervosa are shown in Fig. 1. In each group, the plasma LRH levels reached a steady state 20 to 30 min after beginning of the infusion, and decreased exponentially for 10–12

Table 2.
Distribution volume, metabolic clearance rate and half disappearance time of infused LRH in normal subjects and patients with obesity and anorexia nervosa.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>n</th>
<th>Weight (kg)</th>
<th>DV (l)</th>
<th>MCR (ml/min)</th>
<th>MCR (ml/min/kg)</th>
<th>t½ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4</td>
<td>52.0 ± 1.9</td>
<td>12.1 ± 0.9</td>
<td>1478.9 ± 39.8</td>
<td>28.5 ± 1.2</td>
<td>5.6 ± 0.4</td>
</tr>
<tr>
<td>Obesity</td>
<td>5</td>
<td>84.6 ± 5.6**</td>
<td>20.6 ± 1.5**</td>
<td>2636.6 ± 182.9**</td>
<td>31.3 ± 1.8</td>
<td>5.5 ± 0.2</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>3</td>
<td>34.3 ± 1.8**</td>
<td>6.5 ± 1.1*</td>
<td>621.8 ± 110.5**</td>
<td>17.9 ± 2.4*</td>
<td>7.3 ± 0.1*</td>
</tr>
</tbody>
</table>

Values are means ± SE.
Significant difference from values in normal subjects are indicated (* P < 0.02, ** P < 0.005).
Distribution cessation and achieved were the Table normal higher. The normal constant (28.5 ± 1.6 l/day (1028 ml/min) reported by Jeffcoate et al. (1974), but similar to that of 1640 ± 59.7 ml/min found by Pimstone et al. (1977). Keye et al. (1973) and Jeffcoate et al. (1974) distinguished two phases in the curve for LRH disappearance. Our initial t½ value for normal subjects (5.6 ± 0.4 min) is some-

Discussion

On the other hand, in patients with anorexia nervosa, both the DV and MCR (ml/min and ml/min/kg body weight) of LRH were significantly lower than in normal subjects (P < 0.02). Significant prolongation of the t½ was also noted (P < 0.02).

Fig. 2 shows the correlations between the DV of LRH and the body weight and the percentage deviation from the ideal weight in all the subjects; these correlations show statistically significant positive values of r = 0.958 and 0.947, respectively.

Distribution volume (DV), MCR and t½

Table 2 summarizes the DV, MCR and initial t½ values of synthetic LRH in the three groups. In normal women the DV of synthetic LRH was 12.1 ± 0.9 ml/min, the MCR was 1478.9 ± 39.8 ml/min/kg body weight and the initial t½ was 5.6 ± 0.4 min.

In obese women, the DV and MCR expressed in ml/min were significantly higher than those in normal women (P < 0.005), but the MCR expressed in ml/min/kg body weight and the t½ value were not significantly different from those in normal subjects.

Correlations between distribution volume of LRH and the body weight and percentage deviation from the ideal weight of normal subjects (○) and patients with obesity (●) and anorexia nervosa (▲).
what longer than the values of 2–4 min obtained by Miyachi et al. (1973) and Arimura et al. (1974), but is similar to the values of 5.5–8 min reported by Jeffcoate et al. (1974) and Pimstone et al. (1977). These differences in the values of DV, MCR and t½ may be explained by differences in the methods of its administration (as an infusion or a single bolus injection) and the method of LRH radioimmunoassay.

Values for MCR and t½ differ for different hormones and the metabolisms of some hormones change in diseased states (Sheppard et al. 1979). On infused LRH, Pimstone et al. (1977) observed a significant prolongation of the t½ value and decrease of MCR in patients with impaired renal function, but no significant change was observed in these values in patients with liver dysfunction. Thus they suggested that the kidneys may be a major catabolic organ for this hormone. However, it is necessary to study whether the metabolism of peptide hormones is affected by other factors besides renal function.

Impairment of the plasma GH response in stimulation tests on obese patients has been well documented (Beck et al. 1964; Copinschi et al. 1967), and we also observed a decrease in plasma LH release in the LRH test on obese patients (Chikamori 1976). However, it seems important to determine whether these abnormal responses depend upon a low capacity of the pituitary to secrete hormones, since changes in DV or metabolic clearance of hormones may also cause apparently low response. In the present study the DV and MCR expressed as ml/min were significantly higher in obese patients than in normal subjects, and there was a significant positive correlation between the DV and body weight, or percentage deviation from the ideal body weight, although there was no significant difference in the MCR values expressed as ml/min/kg body weight or the t½ in patients with obesity and normal subjects. If this finding is applicable to pituitary hormones, the low responses of plasma pituitary hormones to stimuli observed in obese patients may be explained, at least in part, by increase in the DV of the hormones.

High plasma levels of GH and cortisol and abnormal responses of these hormones in various loading tests have been observed in many patients with anorexia nervosa (Copinschi et al. 1967; Nishimura et al. 1979). In the present study, the DV and MCR of LRH were significantly less in cases of anorexia nervosa than in normal subjects, with a significant prolongation of the t½. Since a prolongation of the half-life of plasma cortisol has also been observed in patients with anorexia nervosa and malnutrition (Cook et al. 1962), the high plasma levels of GH and cortisol are probably explainable by decrease in the DV values and low disappearance rates of these hormones. In anorexia nervosa, decreases in the serum levels of triiodothyronine and thyroxine and in the basal metabolic rate have been demonstrated (Moshang et al. 1975). Therefore, decrease in metabolism mainly due to impaired thyroid hormone secretion may be one of the causes of decrease in MCR and prolongation of the t½ of LRH in anorexia nervosa.

However, at present LRH release from the hypothalamus cannot be detected, since the level of LRH in the peripheral blood is hardly measurable. Therefore, further studies are required to clarify the significance of changes in metabolism of endogenous LRH in diseased states.

References


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