Comparison between 1 year oral and transdermal oestradiol and sequential norethisterone acetate on circulating concentrations of leptin in postmenopausal women

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BACKGROUND: Oral and transdermal postmenopausal hormone replacement therapy (HRT) affects lipid and glucose metabolism differently, which is of significance in the release of leptin by adipocytes. Moreover, oestrogen and progesterone can stimulate leptin secretion in women of reproductive age. Therefore, we compared the effects of oral and transdermal oestrogen plus progestin regimen on plasma leptin in 38 healthy postmenopausal women with normal body mass index (BMI), who wished to use HRT to control incapacitating climacteric symptoms. METHODS: The women were randomized to treatment with oral HRT (2 mg oestradiol on days 1–12, 2 mg oestradiol plus 1 mg norethisterone acetate (NETA) on days 13–22, and 1 mg oestradiol on days 23–28, n = 19), or with transdermal HRT (50 µg/day of oestradiol on days 1–13, and 50 µg oestradiol plus 250 µg/day NETA on days 14–28, n = 19) for 1 year. Plasma samples were collected before and at oestradiol NETA phase after 2, 6 and 12 months treatment and were assayed for leptin. RESULTS: The baseline leptin, ranging from 3.3 to 34.9 µg/l, was significantly associated with BMI (r = 0.78, P < 0.0001), but showed no difference between women in oral HRT (geometric mean 13.9 µg/l, 95% confidence interval (CI) 10.1–17.6 µg/l) or transdermal HRT group (geometric mean 12.0 µg/l, 95% CI 9.7–14.3 µg/l). Neither oral nor transdermal oestradiol + NETA caused any significant changes in plasma leptin (or BMI) after 2, 6, or 12 months of treatment. CONCLUSION: Leptin is an unsuitable factor to detect oestradiol + NETA-induced metabolic changes in postmenopausal women.

Key words: hormone replacement therapy/leptin/menopause

Introduction

Leptin, produced by adipocytes, is a signal to the central nervous system of the adequacy of energy status of the body (Friedman and Halaas, 1998). The regulation of the production and the release of leptin is not completely understood but lipids, glucose and insulin have been shown to be important determinants of plasma leptin (Boden et al., 1997; Cooling et al., 1998; Saad et al., 1998). Oestrogens may also be factors in this process (Bray and York, 1997). Indeed, oestrogens stimulate the release of leptin in humans (Casebielli et al., 1998) and in rodents (Shimizu et al., 1997). Oestrogens may be one of the factors accounting for higher concentrations of leptin in women than in men (Bray and York, 1997; Saad et al., 1997; Summers et al., 1998) and also for cyclic elevations in leptin concentrations during the menstrual cycle (Hardie et al., 1997; Messinis et al., 1998). In addition, leptin in premenopausal women is higher than that in postmenopausal women (Rosenbaum et al., 1996; Shimizu et al., 1997). Moreover, the use of oestrogen in combination with antiandrogen leads to rises in leptin concentration in transsexual men, but it is not known which component of this combination is responsible for the leptin rise (Elbers et al., 1997). However, the overall data on the impact of oestrogen on leptin are not uniform, because in one study no difference in leptin concentrations was seen between pre- and postmenopausal women and the use of contraceptive pills was associated with no change in leptin concentrations (Castracane et al., 1998). Moreover, natural progesterone can stimulate leptin release and perhaps accounts for higher concentrations of leptin in the luteal than in the follicular phase of the cycle (Hardie et al., 1997; Messinis et al., 1998). Progesterone also stimulates leptin release after ovariectomy, regardless of oestradiol concentrations (Messinis et al., 2000).

Conflicting data exist on the effect of oral hormone replacement therapy (HRT) on leptin in postmenopausal women (Kohrt et al., 1966; Castracane et al., 1998, Elbers et al., 1999, 2001).
Presently, oral HRT and transdermal HRT compete for favour in clinical practice. Due to the lacking first pass liver metabolism of transdermal HRT, responses in the circulating lipids, lipoproteins, and various binding proteins differ in users of oral and transdermal HRT (Hånggi et al., 1997). Therefore, we compared the long-term effects of oral and transdermal oestradiol plus norethisterone acetate administration on the plasma leptin concentrations in healthy postmenopausal women.

Materials and methods

With the approval of the local ethics committee, we studied 38 non-smoking postmenopausal women (last menstrual period >6 months before enrolment, FSH concentrations >30 IU/l, oestradiol concentration <32.7 pg/ml) (Table I). These women formed a subgroup of 63 women, whose vascular reactions to HRT have been reported before (Cacciatore et al. 1998). They had an intact uterus, were otherwise healthy, and used no drugs, but they wished use HRT to control incapacitating climacteric symptoms.

Enrolment took place between 1 January and 30 June. The women were randomized by sealed envelopes to start either oral sequential or transdermal sequential oestradiol/NETA regimen. Values are geometric mean (95% confidence intervals). The regimen led to similar rises in plasma oestradiol concentrations (Cacciatore et al., 1998).

Baseline plasma leptin, ranging from 3.3 to 34.9 µg/l, was similar in both groups and was significantly associated with BMI (r = 0.78, P < 0.0001). Oestradiol + NETA, as a whole, or as considered either as an oral or transdermal regimen separately, failed to affect the plasma leptin concentration or BMI (Table II). Individual (and insignificant) changes in body weight and those in plasma leptin at each study point were not related to each other.

Discussion

Oestrogen is known to stimulate the synthesis of leptin both in humans (Casebielli et al., 1998) and in rodents (Shimizu et al., 1997). In addition, the higher leptin levels in women than in men (Bray and York, 1997; Saad et al., 1997; Sumner et al., 1998), and the elevation in leptin concentrations in pregnancy (Butte et al., 1997; Stock and Bremme, 1998; Laiuvoiri et al., 2000) may be considered as additional evidence for a role of oestrogen in leptin release. Also natural progesterone can stimulate leptin release in fertile-aged women (Hardie et al., 1997, Messinis et al., 1998, 2000). We studied the effect of oestradiol + synthetic progestin (NETA) on plasma leptin in hypo-oestrogenic postmenopausal women, because previous data from postmenopausal women are inconclusive, showing unaffected leptin concentrations during continuous use of oral

Table I. Clinical characteristics of 38 women randomized to start oral or transdermal sequential oestradiol + NETA regimen. Values are mean ± SE

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Transdermal</th>
</tr>
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<tbody>
<tr>
<td>No of women</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.7 ± 0.4</td>
<td>53.2 ± 0.6</td>
</tr>
<tr>
<td>Years after menopause</td>
<td>3.1 ± 0.2</td>
<td>3.2 ± 0.4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.2 ± 0.6</td>
<td>24.7 ± 0.6</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>70.5 ± 5.8</td>
<td>59.8 ± 6.5</td>
</tr>
<tr>
<td>Oestradiol (pg/ml)</td>
<td>10.9 ± 1.9</td>
<td>8.2 ± 2.2</td>
</tr>
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</table>

NETA = norethisterone acetate.

Table II. Plasma leptin concentrations and body mass index (BMI) of 38 women during the combined phase of oral or transdermal oestradiol + NETA regimen. Values are geometric mean (95% confidence intervals)

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Transdermal</th>
</tr>
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<tbody>
<tr>
<td>Plasma leptin (µg/l)</td>
<td>13.9 (10.1–17.6)</td>
<td>12.0 (9.7–14.3)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 (24.9–27.4)</td>
<td>24.7 (23.5–25.9)</td>
</tr>
<tr>
<td>2 months</td>
<td>14.2 (11.7–16.7)</td>
<td>13.0 (10.0–15.9)</td>
</tr>
<tr>
<td>6 months</td>
<td>15.3 (11.8–18.9)</td>
<td>14.6 (10.6–18.6)</td>
</tr>
<tr>
<td>12 months</td>
<td>14.8 (11.1–18.5)</td>
<td>13.5 (10.6–16.4)</td>
</tr>
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All samples were run in the same batch of the assay to eliminate the effect of interassay variation, and the intra-assay coefficient of variation was 3.8% at the concentration level of 15.6 µg/l.

The leptin data were skewed and were therefore log transformed before analyses. The data (presented as mean ± SEM) were analysed by two-way analysis of variance (ANOVA) with repeated measurements. When indicated by ANOVA, the significance at individual time points was calculated using the t-test for independent means (between group comparison), or the t-test for dependent means (comparison with baseline within a single group). Pearson’s correlation was used for correlation analyses. A power calculation showed that this population was large enough to detect a 15% change in leptin with 87% power at a P-level of 0.05.
conjugated oestradiol plus medroxyprogesterone regimen (Kohrt et al., 1996), similar concentrations of leptin in women with and without HRT (Castracane et al., 1998), an elevation in leptin following 2 months oral use of oestradiol (Elbers et al., 1999), or reduced leptin during the use of different unspecified HRT regimens (Di Carlo et al., 2000).

In addition, we compared the effect of oral and transdermal HRT regimens on plasma leptin, because they are known to affect to different extents both lipids and lipoproteins (Hänggi et al., 1997) and perhaps also some other biological mediators. For instance, oral HRT causes a greater decrease in total and low-density lipoprotein cholesterol concentrations but a greater increase in triglycerides than does transdermal HRT (Hänggi et al., 1997). It is also known that HRT in postmenopausal women can cause modest although often transient rises in body weight (Lubbert and Nauert, 1997), and this effect can be more marked during the use of transdermal HRT (Lubbert and Nauert, 1997; Espeland et al., 1998; Hänggi et al., 1998). However, the general scientific consensus is that HRT does not increase body weight but may instead prevent or reduce the age-induced rise in body weight (Chmouilovsky et al., 1999; Sayegh et al., 1999).

Our data are in agreement with this opinion, because no change in body weight was seen during the first year of the use of oral or transdermal HRT (Table II).

The plasma leptin concentration is co-dependent on leptin synthesis by the adipocytes (Zhang et al., 1994) and renal clearance of leptin (Cumin et al., 1997). Because HRT, as a whole, or oestradiol + NETA do not alter renal function, any change in plasma leptin concentration observed during oestradiol + NETA may primarily be a reflection of the change in synthesis and release of leptin. Neither oral nor transdermal sequential oestradiol + NETA affected plasma leptin in our subjects. Thus, we can conclude that this combination did not affect the synthesis or release of leptin in our group of postmenopausal women. The lack of an effect of oestradiol + NETA on leptin was a surprise because natural progesterones stimulate leptin release in oestrogen-primed women (Hardie et al., 1997; Messinis et al., 1998, 2000). We did not have a control group using placebo, and therefore the impact on leptin of age over the 12 months of the study remains unknown. However, leptin has shown no age dependence in some studies (Saad et al., 1997; Sumner et al., 1998), and therefore the lack of a control group is unlikely to invalidate our conclusions.

Our findings should be interpreted with caution. We collected plasma samples during oestradiol + NETA phase, and therefore our data do not exclude the possibility that leptin concentrations could have shown a rise during the oestradiol-only phase of HRT and that NETA could have negated this effect. This is supported by the androgenic activity of NETA, and by data demonstrating that androgens decrease leptin secretion (Elbers et al., 1997). Moreover, our data do not tell anything of the effect of other HRT regimens containing different oestrogens and/or progestins on leptin. HRT can also involve the use of natural progesterone, and its impact on leptin in postmenopausal women is of interest, because natural progesterone stimulates leptin in women immediately after oophorectomy (Messinis et al., 1999, 2000).

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References


Hormone replacement therapy and circulating leptin


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