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Plasma β-Endorphin Levels in Patients with Gynaecological Malignancies

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THE OPIOID neuropeptide β-endorphin is present in the peripheral blood at a concentration estimated between 10^{-11} and 10^{-12} mol/l [1, 2]. Likewise, the five-amino acid N-terminal fragment, met-enkephalin, is also present in plasma at concentrations ranging from 10^{-11} to 10^{-10} mol/l [3]. Opiate receptors and specific non-opiate receptors have also been reported on peripheral blood monocytes, granulocytes, and lymphocytes [4] indicating that these immune cells may be target for circulating peripheral opioid peptides.

We attempted to determine plasma β-endorphin levels in patients with gynaecological malignancies and compare them to those in healthy women. Blood samples from 6 healthy women (median age, 45; range, 32–37), 11 patients with ovarian carcinoma (median age, 43; range, 19–68), and 5 patients with uterine carcinoma (median age, 48; range, 30–56) were collected early morning on bed rest. The blood (8–10 ml), collected in siliconised glass tubes containing EDTA, was immediately centrifuged and plasma frozen at −20°C until assayed. β-Endorphin was extracted by an affinity gel extraction method using sepharose adsorption particles, and then measured by radioimmunoassay (β-endorphin RIA kit, NEN Research Products, DuPont, France). Assays were performed in duplicate and the results were averaged. The intra- and interassay coefficients of variations of this radioimmunoassay were 8.6 and 9.1%, respectively. The results were presented as the mean ± S.D. Statistical analysis of the results was performed using the Student's *t*-test for paired and unpaired data, and the analysis of variance.

As shown in Fig. 1, plasma β-endorphin levels of patients with gynaecological malignancies were significantly higher than those of healthy women. This is, to our knowledge, the first report describing a significant increase in plasma β-endorphin levels in cancer patients. These results suggest that β-endorphin may be involved in development of gynaecological malignancies through modulation of cellular immunity. It has been suggested that natural cytotoxicity in humans and nude mice can be enhanced by opioid peptides probably acting through opiate-specific mechanisms [5]. Accordingly, it is conceivable that endorphins (including enkephalins) play a crucial role in immune surveillance mechanisms. Hazum *et al.* [4] reported that a

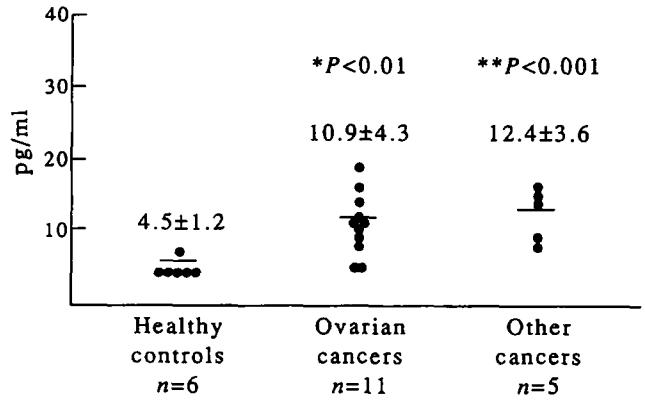

Fig. 1. Plasma β-endorphin levels in healthy women and patients with gynaecological malignancies. Figures on columns show the mean ± S.D. *$P < 0.01$, **$P < 0.001$ (Student's *t*-test), compared with healthy controls.

molecule such as β-endorphin may bridge two sub-types of lymphocyte by binding through its COOH-terminus to an opiate receptor on another lymphocyte. Concentrations of 1 nmol/l endorphins and 10 nmol/l met-enkephalin which did not affect cell proliferation and viability as described previously [6] have been exclusively used in this study. These concentrations seemed to be high, compared to physiological levels of β-endorphin. However, corticotropin-releasing factor (CRF) has been observed to cause the *de novo* synthesis and release of leucocyte-derived β-endorphin [7]. Blalock [8] has also reviewed that the endogenous opiates are locally produced by cells of the immune system and thereby reach high levels. In addition, Carr *et al.* [9] have recently shown that CRF will increase natural killer activity through its ability to induce leucocyte-derived endorphins.

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