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Circulating levels of β-endorphin and cortisol in breast cancer

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ABSTRACT

Neurobehavioral stress can promote the growth and progression of different types of cancer because psychological factors can alter immune and endocrine function. β-endorphin is one of the hormones involved in the bidirectional connection between the immune and neuroendocrine systems that explains the effects of stress on the immune capacity against cancer. Breast cancer (BC) is the most common type of cancer in women and one of the best known to influence the different stressors involved in coping with the disease. Here we evaluated the circulating levels of β-endorphin and cortisol in premenopausal and postmenopausal women with BC treated or not with neoadjuvant chemotherapy, to understand the neuroendocrine basis that explain the relationship between stress and the development of the disease. In our hands, healthy women show elevated levels of β-endorphin, levels that are even higher in postmenopausal women. In women with BC, however, significantly lower levels appear, with no differences between premenopausal and postmenopausal women. These data correlate with cortisol levels, which are much higher in women with BC regardless of their hormonal status. Neoadjuvant chemotherapy treatment only improves β-endorphin levels in postmenopausal women, without recovering the levels of healthy women. In women treated with neoadjuvant chemotherapy, both premenopausal and postmenopausal maintain elevated cortisol levels that are indicative of the stressful situation. Regulation of stress levels by modulation with β-endorphin could be an alternative pharmacological therapy against tumor growth and development, as well as its ability to promote in patients feelings of well-being that improve the development of their disease.

1. Introduction

An important research objective is to verify the relationship between the nervous system and cancer [16], that is, to try to demonstrate the connection between the psychological characteristics of the person due to stressful situations in life and the occurrence of cancer or its evolution. Recent evidence shows that neurobehavioral stress can promote the growth and progression of different types of cancer [12,17,18,20]. Psychological factors can alter immune and endocrine function, and it is well known that through these pathways, stress can affect tumor growth and spread. Similarly, stress relief for people with cancer promotes a faster recovery or a feeling of feeling better in those patients receiving radiation therapy or chemotherapy [11].

In this sense, opioid peptides have been proposed as those responsible for causing immunological alterations sufficiently important to promote the appearance or growth of tumors [3,10]. In fact, several facts support this hypothesis, such as the expression of various opioids and their receptors in tumor tissue. However, the various studies carried out in animals and humans have led to conflicting results [17,18].

One of these opioid peptides is β-endorphin, which can be considered as one of the hormones involved in the bidirectional connection between the immune and neuroendocrine systems that could explain the effects of stress on the immune capacity against cancer [17,18].

Breast cancer is the most common type of cancer in women and one of the best known to influence the different stressors involved in coping with the disease [8]. In the present study, we evaluated the circulating

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levels of β-endorphin and cortisol in premenopausal and postmenopausal women with breast cancer, treated or not with neoadjuvant chemotherapy, to try to understand the neuroendocrine basis that allows to explain the relationship between the stress and the development of the disease, as well as promoting therapies that help prevent or slow down the development of the disease.

2. Material and methods

2.1. Subjects and study design

A total of 198 women were recruited at the Unit of Breast Pathology at the University Hospital of Jaén, and 78 volunteers women without breast cancer were also included as control groups. This study was approved by the Ethical Committee of the University Hospital of Jaén and all subjects signed a term of free, informed consent.

Patient characterization included age at diagnosis, tumor size, tumor histology, pathologic T classification, Scarff–Bloom–Richardson grade, hormonal and HER-2/neu status, and molecular subtype. All women with breast cancer were diagnosed with ductal infiltrating carcinoma. A total of 83 of these women (39 premenopausal and 44 postmenopausal) did not receive neoadjuvant chemotherapy, whereas 115 of them (63 premenopausal and 52 postmenopausal) received neoadjuvant chemotherapy before surgery. The clinicopathological characteristics of studied patients have been previously reported [15] and are shown in Table 1. Patients treated with neoadjuvant chemotherapy received an anthracycline/taxane-based regimen including 4 courses of EC (epirubicin 90 mg/m2 and cyclophosphamide 600 mg/m2, every 21 days), followed by 8 courses of 100 mg/m2 paclitaxel once a week or 4 courses of 75 mg/m2 docetaxel every 21 days. Patients with a HER2/neu-overexpressing tumor also received trastuzumab (14 courses at 6 mg/kg every 21 days). Women with triple-negative breast cancer received 6 cycles of 75 mg/m2 docetaxel plus carboplatin (AUC 6).

Control groups consisted of 78 women, aged 28–69 years old (premenopausal women with regular menstrual periods n = 38; postmenopausal women with spontaneous menopause for at least one year, n = 40), with no previous history of any type of cancer, chemotherapy, hormonal or antioxidant therapy, or chronic diseases. Thus, women were excluded if they were current smokers, regular alcohol consumers, antioxidant supplement users, pregnant or lactating, presented hepatic, cardiac or renal dysfunction, hormonal therapy, use of drugs, hypertension, diabetes, and other eventual chronic conditions.

Table 1
Clinicopathological description of the patients involved in this study.

	Premenopausal		Postmenopausal	
	Untreated	Neoadjuvant chemotherapy	Untreated	Neoadjuvant chemotherapy
Characteristics	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Age (years)	45.2 ±	45.1 ± 0.8	65.3 ±	65.3 ± 0.90
Mean	1.2	46	0.9	63
Median	48	29–53	64	56–78
Range	27–54		57–78	
Tumor histology	39	63 (100%)	44	52 (100%)
Ductal	(100%)	0 (0%)	(100%)	0 (0%)
Lobular	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)		0 (0%)	
Molecular	23	34 (54.0%)	27	27 (51.9%)
subtypes	(59.0%)	7 (11.1%)	(61.4%)	12 (23.1%)
Luminal A	10	18 (28.6%)	6 (13.6%)	0 (0%)
Luminal B	(25.6%)	4 (6.3%)	4 (9.1%)	13 (25.0%)
Her-2	2 (5.1%)		7 (15.9%)	
Triple negative	4 (10.3%)			
Pathologic	1.31 ±	3.02 ± 0.17	1.52 ±	3.36 ± 0.15
tumor size	0.09	3.00	0.14	3.00
(cm)	1.20	0.8–5.6	1.30	1.4–5.0
Mean ± SEM	0.5–3.1		0.8–5.0	
Median				
Range				
Pathologic T	0 (0%)	0 (0%)	0 (0%)	0 (0%)
classification	35	18 (28.6%)	40	6 (11.5%)
0	(89.7%)	40 (63.5%)	(90.9%)	43 (82.7%)
1	4 (10.3%)	5 (7.9%)	4 (9.1%)	3 (5.8%)
2	0 (0%)		0 (0%)	
3				
Scarf-Bloom-	19	8 (12.7%)	10	13 (25%)
Richardson	(48.7%)	55 (87.3%)	(22.7%)	39 (75%)
grade	20	0 (0%)	34	0 (0%)
I	(51.3%)		(77.3%)	
II	0 (0%)		0 (0%)	
III				
Hormonal Status	33	41 (65.1%)	33	36 (69.2%)
ER+	(84.6%)	22 (34.9%)	(75.0%)	16 (30.8%)
ER-	6 (15.4%)	41 (65.1%)	11	33 (63.5%)
PgR+	25	22 (34.9%)	(25.0%)	19 (36.5%)
PgR-	(64.1%)		27	
	14		(61.4%)	
	(35.9%)		17	
			(38.6%)	
HER-2/neu	29	38 (60.3%)	34	49 (94.2%)
status	(74.4%)	25 (39.7%)	(77.3%)	3 (5.8%)
Negative	10		10	
Positive	(25.6%)		(22.7%)	

2.2. Sample acquisition

Samples from patients treated with neoadjuvant chemotherapy were obtained with in a week after completion of chemotherapy treatment and in parallel to samples from untreated patients and control volunteers in order to be processed under the same conditions.

Blood samples were obtained after an overnight fast by venous arm puncture in tubes without anticoagulants. Blood specimens were allowed to cloth and centrifuged at 3000 g, for 10 min, at 4 °C to obtain the serum. Serum samples were collected, rapidly frozen in liquid nitrogen and kept on −80 °C until usage for assays.

2.3. β-endorphin assay

Samples were measured by a human β-endorphin ELISA kit (Cusabio), according to manufacturer instructions. The sensitivity of detection is 15.6 pg/mL; intra-assay coefficient of variation is <8%; inter-assay coefficient of variation is <10%.

2.4. Cortisol assay

Samples were measured by fluorescence polarization immunoassay (FPIA) for the quantitative measurement of cortisol (Abbot Axsym System, Germany), according to manufacturer instructions. The sensitivity of detection is < 1.1 μg/dL; intra-assay coefficient of variation is <6.5%; inter-assay coefficient of variation is <6%.

2.5. Statistical analysis

Differences between groups were analyzed by two-way analysis of variance plus LSD post-hoc test, using IBM SPSS V.23 software. All comparisons with p-values below 0.05 were considered significant.

3. Results

Fig. 1A shows the results obtained in the circulating levels of β-endorphin in pre- and postmenopausal control women and pre- and postmenopausal women with breast cancer treated or not with neoadjuvant chemotherapy. A significant increase ($p < 0.01$) in β-endorphin levels have been found in healthy postmenopausal women when compared to premenopausal healthy women. On the contrary, both pre- and postmenopausal untreated women with breast cancer showed significant ($P < 0.001$) lower levels of β-endorphin and without differences according to the hormonal status. In the same way, significant lower

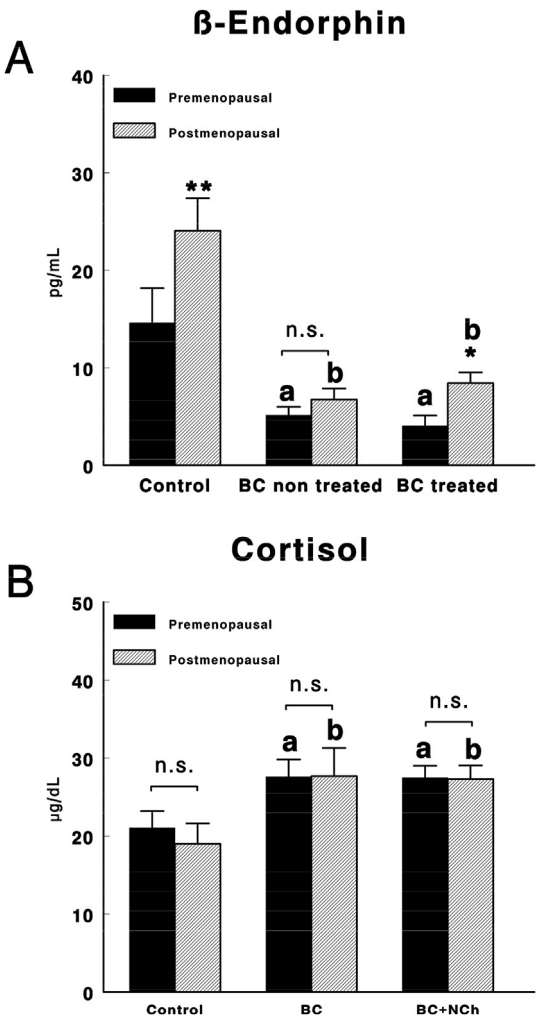

Fig. 1. Circulating levels of β-endorphin (A) and cortisol (B) measured in healthy premenopausal and postmenopausal control women, premenopausal and postmenopausal women with breast cancer (BC) and premenopausal and postmenopausal women with breast cancer (BC) treated with neoadjuvant chemotherapy (Mean ± SEM; *$p < 0.05$, **$p < 0.01$ premenopausal vs. postmenopausal women; $^{a}p<0.01$ vs. premenopausal control women; $^{b}p < 0.01$, vs. postmenopausal control women).

levels of β-endorphin were found in premenopausal women with breast cancer treated with neoadjuvant chemotherapy, whereas postmenopausal treated women showed a slight increase in circulating β-endophin levels when compared with premenopausal women with breast cancer treated with neoadjuvant chemotherapy (Fig. 1A).

Fig. 1B shows the results obtained in the circulating levels of cortisol in pre- and postmenopausal control women and pre- and postmenopausal women with breast cancer treated or not with neoadjuvant chemotherapy. No significant differences were found in cortisol levels between pre- and postmenopausal healthy women, women with breast cancer or women with breast cancer treated with neoajuvant chemotherapy. However, a significant increase ($p < 0.001$) in cortisol levels have been found in both pre- and postmenopausal untreated women with breast cancer and in women with breast cancer treated with neoadjuvant chemotherapy (Fig. 1B).

No significant correlations were found between cortisol and β-endorphin levels for none of the group analyzed.

4. Discussion

Several studies suggest that the neuroendocrine response of the body that originates as a consequence of physical or psychosocial stress can affect various aspects of immune function and promotes a decrease in immune surveillance that decreases the processes that protect against cancer such as repair of the DNA or the regulation of cell growth [2,3,17,18,20]. β-endorphin has been postulated as one of the opioid peptides responsible for reducing stress and therefore promoting the prevention of cancer growth and progression. In fact, in animal models it has been well demonstrated that the reduction of the stress response by β-endorphin cell transplantation may prevent cancer growth and progression [19]. Thus, body's psychophysiological reactions during stress are associated with a greater likehood of incidence or relapse of cancer [3,12] due to the production of several inflammatory cytokines which may promote cancer growth and progression at biochemical and molecular levels [9] and a variety of immunological mechanisms [1,5,13,21,22].

In this sense, our results show that, indeed, healthy women show elevated levels of β-endorphin that are even higher in postmenopausal women. In women with breast cancer, however, significantly lower levels appear, with no differences between premenopausal and postmenopausal women. These data in turn correlate with cortisol levels, which are much higher in women with breast cancer regardless of their hormonal status.

On the other hand, neoadjuvant chemotherapy treatment only improves β-endorphin levels in postmenopausal women but not in premenopausal women, although without recovering at all the levels typical of healthy women, which suggests that treated postmenopausal women tend to feel better that treated premenopausal women, who seem to be unable to overcome the level of stress caused by the disease [11]. β-endorphin is known to have the ability to inhibit stress hormone production and produce analgesia and a feeling of well-being [7]. Low β-endorphin, on the contrary, is connected with psychiatric disorders and depression [4,6]. However, in women treated with neoadjuvant chemotherapy, both premenopausal and postmenopausal women maintain elevated cortisol levels that are indicative of the stressful situation that these people continue to experience, and that therefore does not facilitate an inhibition of the factors that could suppress an adequate immune response as a consequence of stress.

Therefore, the regulation of stress levels by modulation with β-endorphin is defined as an alternative pharmacological therapy that is worth studying for its possibilities against tumor growth and development, as well as its ability to promote in patients feelings of well-being that improve the development of their disease. This control of body's stress response may be beneficial against cancer.

5. Limitations of the study

In addition to the limitations inherent to cross-sectional studies, we have not information about the stage of the menstrual cycle in premenopausal women. However, a detailed description of the circulating levels of LH, FSH, GnRH, estradiol, and progesterone have been previously described [14]. Finally, it should be noted that the present work does not have data on mood disorders or perceived stress in the population under study to exactly correlate with the endocrine changes found here.

Conflict of interest

None to declare.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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