Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 867–870
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Metabolism of histamine in tissues of primary ductal breast cancer

Jarosław von Mach-Szczypiński, Stanisław Stanosz*, Krzysztof Sieja, Małgorzata Stanosz

Department of Menopause and Andropause, Pomeranian Medical University in PL-71-256 Szczecin, Poland

Received 27 May 2008; accepted 5 February 2009

Abstract

Histamine performs an important role in the pathologic and physiologic aspects of the breast gland. Among monoamines, histamine demonstrates the greatest proliferative activity in breast cancer. The aim of the study was to evaluate histamine concentration in plasma and tissues of breast cancer dependent on the activity of histamine metabolism enzymes in neoplasmatic tissues of the breast gland. Ninety-five women aged 38 to 70 years were divided into 2 groups. The control group (group I) consisted of 30 healthy women. Group II consisted of 65 women with primary ductal breast cancer. The concentration of histamine in plasma was assessed by immunoenzymatic method. The concentration of histamine in cancerous tissues of the breast and the metabolism of histamine enzymes, specially histidine decarboxylase, decarboxylase of aromatic L-amino acids, *N*-histamine methyltransferase, monoamine oxydase B, and diamine oxydase, were determined using isotope technique. In the course of 24 hours, excretion of *N*-methylimidazoleacetic acid was evaluated by the methods of chromatography. The statistical analysis was made based on Statistica Pl Ed (StatSoft, Cracow, Poland, 1998). A significant increase in the concentration of histamine in plasma ($P < .01$) and tissues of ductal breast cancers ($P < .001$), and in the activity of histidine decarboxylase ($P < .01$), aromatic L-amino acids ($P < .05$), and histamine methyltransferase ($P < .05$) was found. Activity of monoamine oxidase B ($P < .01$) and diamine oxidase ($P < 0.01$) and excretion of *N*-methylimidazoleacetic acid were significantly decreased compared with the control group ($P < 0.001$). The conclusions are as follows: (1) Concentration of histamine in the plasma of women is dependent on the concentration of histamine in the tissues of ductal breast cancers. (2) The significant increase of histamine in cancerous tissues of ductal breast cancer could suggest the participation of this monoamine in the development of breast cancer. (3) The increase of histamine concentrations in ductal breast cancer tissues can be connected with the disturbances of the balance between synthesis and enzymatic inactivation of this monoamine. (4) The concentration of histamine in the plasma of women with ductal breast cancers is dependent on the number of involved lymph nodes and the grade of histologic malignancy.

1. Introduction

There are several factors for the effect of histamine (HA) in cancer. Some cancer cell lines have been shown to have functional HA receptors and can be stimulated by local HA administration. Histamine also has important effects on immune cells. Histamine has been demonstrated to mediate growth control mechanisms in experimental mammary carcinoma, specifically by acting on certain H_2 membrane receptors [1]. Histamine acts directly through H_1- and H_2-receptors onto the proliferation and early expression of cell response, leading to the increase of enzymatic activity of the cells and their metabolism. The proliferative activity of HA changes in the mammary gland leads to an interaction with the epidermal growth factor and other growth and hormonal factors [2]. Endogenous HA has been shown to affect growth mechanisms in experimental mammary carcinomas via H_2-membrane receptors. Both H_1- and H_2-binding sites are present in human mammary glands, but only 75% of malignant carcinomas express H_2-receptors.

Histamine is an important mediator of immunologic reactions of breast glands and is involved in the development of precancerous and cancerous states of the breast [3,4]. Because there were too few reports on HA and the conclusions were undecided, the authors were motivated to evaluate the concentration of HA in the neoplasmatic tissues of ductal breast cancers and the activity of enzymes taking place in the metabolism of HA [4,5].

2. Objective

The aim of the study was to evaluate HA concentration in plasma and tissues of breast cancer dependent on the activity

* Corresponding author. Tel.: +48 91 487 3225; fax: +48 91 425 33 06.
E-mail address: magnum@med.pam.szczecin.pl (S. Stanosz).

0026-0495/$ – see front matter © 2009 Published by Elsevier Inc.
doi:10.1016/j.metabol.2009.02.011

of HA metabolism enzymes in neoplasmatic tissues of the breast gland.

3. Material and methods

The material comprises 95 women aged 38 to 70 years divided into 2 groups. The controls (group I) consisted of 30 healthy women without changes in the breast glands (mean age, 50.5 ± 6.3 years) in whom mammoplasty operations were performed. The histopathologic material was taken during surgery. These women reported no complaints from breast glands. In these women, clinical, ultrasonographic, and mammographic examinations showed no pathologic changes. No changes were revealed in histopathologic specimens. The control group was submitted to biochemical analysis of unchanged tissue specimens. Study group II consisted of 65 women (mean age, 53.9 ± 7.1 years) with ductal breast cancer. Mastectomy was performed, and the diagnosis was confirmed by histopathologic examination (Table 1). In this group, clinical and histologic assessment of breast cancer in women was made.

Before the operation, blood samples were taken from an antecubital vein in the morning hours to evaluate HA concentration in the plasma. The women in both groups had venous cannulae inserted into the basilar veins. Samples of venous blood for biochemical tests were taken after a fasting period during the night until 8:00 AM. Blood for the estimation of concentrations of HA was collected into a syringe containing anticoagulants and antioxidants (KB Labortechnik, Reutlingen, Germany). The concentration of HA in the blood plasma was determined by an enzyme-linked immunosorbent assay method with reagents kits (Immunotech, Marselline, France). An exact description of the method is provided in the manufacturer's instructions (Histamine Enzyme Immunoassay Kit, 2015). The specimens of normal breast tissues (in the control group) and cancerous tissues (in the study group) were taken during surgery. Samples of healthy tissues of the breast glands were taken during mammoplasty and samples of ductal breast cancer were taken during mastectomy to study HA concentration and activities of the enzymes. The obtained surgical specimens weighed 3 to 5 g. These surgical specimens were instantaneously frozen in liquid nitrogen for 5 minutes. This was done while the surgeon was operating on the patient. Subsequently, these specimens were wrapped up in foil and stored in the refrigerator at a temperature of −80°C. In these surgical specimens were analyzed the concentration of HA and its enzymes. The concentration of HA in specimens was determined using isotope technique [6]. The activity of histidine decarboxylase (HDC, EC 4.1.1.22) and decarboxylase aromatic L-amino acids (AADC, EC 4.1.1.28) in tissues was assessed by isotopic method [7]. Diamine oxidase (DAO, EC 1.4.3.6) and monoamine oxidase B (MAO-B, EC 1.4.3.4) activities in the breast tissue specimens were assessed by means of isotope technique according to the method described by Fogel et al [8]. The activity of HA *N*-methyltransferase (HMT, DC 2.1.1.8) was measured by the Snyder and Axelrod method [9]. During the course of 24 hours, excretion in urine of telemethylimidazoleacetic acid (MIAA) was analyzed by the liquid high-pressure chromatography method of Søndergaard [10]. Nuclear estrogen receptors were studied by the immunohistochemical method using LSAB sets (Dako, Copenhagen, Denmark). The morphologic examinations of the tissues were performed in the Cathedral of Pathomorphology Pomeranian Medical University in Szczecin. The biochemical analyses were performed in the Department of Biogenic Amines of the Polish Academy of Science in Łódź and the Medical Laboratory in Bremen (Germany). This clinical study has been carried out with the approval of the ethical committee. To perform this study, we received as well the agreement of the Bioethical Committee of Pomeranian Medical University (Nr BN-001/150/03).

The obtained results were statistically evaluated by means of the set Statistica PL version number 5 (StatSoft, Cracow, Poland). The studied groups were compared with the Student *t* test. The results were analyzed using the Wilcoxon test for nonparametric data. Results were considered to be statistically significant when P was less than .05.

Table 1
Clinical and histologic assessment of breast cancer in women (n = 65)

Parameters	n	%
Age		
<40 y, premenopausal	5	7.7
>40 y, premenopausal	20	30.7
>48 y, postmenopausal	40	61.5
BMI <25 kg/m^2	19	29.3
BMI >25 kg/m^2	46	70.7
Diameter of neoplasmatic changes		
T_1 <2 cm	21	32.2
T_2 2 cm	15	23.1
T_3 >2 cm	29	44.6
Grades of histologic malignancy according to Bloom and Richardson		
I°	17	26.1
II°	37	56.9
III°	11	16.9
Histologic types		
Ca. ductale	57	87.7
Ca. lobulare	5	7.7
Ca. cribriforme	3	4.6
ER status		
ER (+)	57	87.7
ER (−)	8	12.3
Status lymph nodes		
N_0–without lymph node involvement	23	35.4
N_1 and N_2–with lymph node involvement	42	64.6
1-3 Lymph nodes	25	59.5
4-6 Lymph nodes	12	28.5
>6 Lymph nodes	5	11.9
N_3–with supraclavicular nodes involvement on the side of the breast cancer	7	16.6

BMI indicates body mass index; ER, estrogen receptor.

4. Results

Results of the study are presented in Tables 1 to 3. Table 1 reveals the clinical and histopathologic studies of breast cancer patients. Table 2 presents the activity of HA and their enzymes in cancerous tissues of the study group vs control group. Table 3 presents the concentration of HA in plasma of patients with breast cancer dependent on diameter, histologic malignancy, and the involvement of regional lymph nodes.

Table 3
The concentration of HA in plasma ductal breast cancer tissue dependent on size, histologic malignancy, and involvement of regional lymph nodes

Parameters	n	HA, nmol/L	*P* value
Diameter of the breast cancer			
<2 cm	21	13.3 ± 5.1	NS
2 cm	15	14.1 ± 5.4	NS
>2 cm	29	14.5 ± 7.3	NS
Grades of histologic malignancy according to Bloom and Richardson			
I°	17	12.1 ± 2.7	NS
II°	37	15.3 ± 5.2	<.05
III°	11	17.9 ± 3.5	<.01
Status of lymph nodes			
N_0–without lymph node involvement	23	12.2 ± 4.1	NS
N_1 and N_2–with lymph node involvement	42	16.9 ± 2.4	<.01
1-3 Lymph nodes	25	15.2 ± 3.9	<.05
4-6 Lymph nodes	12	17.5 ± 2.1	<.01
>6 Lymph nodes	5	17.8 ± 1.4	<.001
N_3–with supraclavicular nodes involvement on the side of the breast cancer	7	18.3 ± 3.7	<.001

NS indicates not significant.

5. Discussion

The significantly higher HA concentration in serum ($P < .01$) and neoplasmatic tissues of ductal breast cancer ($P < .001$) than in those of the control group in the present study suggests the role of this monoamine in the etiopathogenesis of neoplasm [3,5,11,12]. The significant increase in HA concentration in ductal breast cancers is caused by the enhanced biosynthesis of HA from histidine. As found in the present study, the increased activity of HDC ($P < .01$) and AADC ($P < .05$) leads to an increase in the biosynthesis of HA in tissues of ductal breast cancer ($P < .001$).

The metabolism of HA in the organism takes place in 2 metabolic ways: one is methylation, and the second is oxidation. Two enzymes [12,13] are involved, namely, HMT and DAO. *N*-methyltransferase catalyzes the transformation of tissue HA to telemethylhistamine by the process of methylation [12]. In the study group, the activity of HMT was significantly higher than that in the control group ($P < .05$). The biotransformation of HA by means of oxidative deamination is catalyzed by DAO. Diamine oxidase is the main enzyme for the metabolism of ingested HA [13]. The activity of DAO in tissues of ductal breast cancer was significantly lower than that in the control group ($P < .01$). The decreased DAO activity in cancerous tissues of breast cancer when compared with unchanged tissues of the breast glands of healthy women suggests a lowering of HA inactivation in these tissues of the breast cancer. Monoamine oxidase B takes place in the oxidation process [14]. In the study group, the activity of MAO-B was significantly lower ($P < .01$) than that in the control ($P < .01$).

In the degradation of HA are also involved aldehyde dehydrogenase, aldehyde oxidase, and xanthine oxidase, which catalyze telemethylimidazoleacetic aldehyde to MIAA and imidazoleacetic aldehyde to imidazoleacetic acid.

The statistical increase of HA concentrations in the plasma ($P < .01$) and neoplasmatic tissues of ductal breast cancer ($P < .001$) could be caused by disturbances of the balance between the biosynthesis and biodegradation processes. Statistically, a daily lowering of excretion in urine of MIAA was found in the study group ($P < .001$). This acid is the end-product of HA degradation during methylation.

In the present study, significantly higher HA concentration was found in the neoplasmatic tissues of ductal breast cancer patients than in the healthy women ($P < .001$), which can suggest the role of this monoamine in the pathogenesis of breast cancer disease. Local intensive metabolism of HA takes place in breast cancer tissues, which is expressed by high concentration of HA in these tissues [3,5,11-13]. Histamine may be also a by-product of the mast cell infiltration into the existing cancer [15]. Significant increase of the HA concentration in neoplasmatic tissues in ductal

Table 2
Concentration of HA and activity of HA enzymes in neoplasmatic tissues of ductal breast cancer in women (n = 65)

Parameters	Abbreviation	Range		$x \pm SD$		*P* value
		Group I	Group II	Group I	Group II	
Histamine in plasma, nmol/L	HA	3.5-6.1	5.2-14.3	5.92 ± 3.1	8.23 ± 3.4	<.01
Histamine in tissue, nmol/g tissue	HA	4.8-6.99	9.1-17.1	6.34 ± 2.7	14.2 ± 5.1	<.001
Histidine decarboxylase, pmol/mg tissue	HDC	29-44	30-64	39.3 ± 26.9	54.7 ± 17.1	<.01
Decarboxylase aromatic L-amino acids, pmol/g tissue	AADC	19-30.1	22-48	24.1 ± 9.7	34.4 ± 14.2	<.05
Histamine methyltransferase, pmol min^{-1} mg^{-1} tissue	HMT	22-43	29-77	33.9 ± 25	61.3 ± 45.7	<.05
Monoamine B oxydase, pmol min^{-1} mg^{-1} tissue	MAO-B	89-151	71-124	135.3 ± 69.8	99.3 ± 44.6	<.01
Diamine oxydase, pmol min^{-1} mg^{-1} tissue	DAO	25-42	1-22	36.1 ± 9.7	14 ± 6.4	<.01
Methylimidazoleacetic acid, mg/24 h	MIAA	1.9-3.1	0.3-2.4	2.58 ± 0.8	1.44 ± 0.5	<.001

$P < .05$: level of significance.

breast cancers is caused by the increased biosynthesis of HA from histidine. The result is a significantly higher activity of HDC ($P < .01$) and nonspecific AADC ($P < .05$) and, simultaneously, the decrease of the activities of DAO ($P < .01$) and MAO-B ($P < .01$).

In general, significantly higher concentration of HA in tissues of ductal breast cancer resulted from higher synthesis of HA and lower catabolic processes. The results of our research highlight the fact that intracellular HA metabolism varies in healthy and malignant tissues [3,11,12].

The obtained results indicate that, in the development of ductal breast cancer, there are essential changes in the activity of enzymes involved in the biotransformation of HA. The observed changes result from the neoplasmatic process in tissues of breast gland.

The concentration of HA in the plasma and neoplasmatic tissues is independent of the diameter of the ductal breast cancer [15]; but there is a dependence between the histologic malignancy and the number of involved lymph nodes from one side, and the concentration of HA in neoplasmatic tissues [11]. Results revealed in Table 3 suggest that, with the progression of the ductal breast cancer, the disturbances in HA metabolism are on a greater scale [16]. Recent articles of della Rovere et al [14] and Rajput et al [17] show that increased mast cell infiltration per se appears to correlate with lower tumor grade and improved prognosis.

6. Conclusions

1. The concentration of HA in the plasma of women is dependent on the concentration of HA in the tissues of ductal breast cancer.
2. The significant increase of HA in cancerous tissues of ductal breast cancer could suggest the participation of this monoamine in the development of breast cancer.
3. The increase of HA concentrations in ductal breast cancer tissues can be connected with the disturbances of the balance synthesis and enzymatic inactivation of this monoamine.
4. The concentration of HA in plasma of women with ductal breast cancer is dependent on the number of involved lymph nodes and the grade of histologic malignancy.

Acknowledgment

The authors thank Prof W Domagała, MD, the head of the Cathedral of Pathomorphology Pomeranian Medical University in Szczecin; Prof A Fogel, MD, the head of the Department of Biogenic Amines of Polish Academy of Sciences in Łódź; and A Gerritzen, MD, of the Medizinische Labor in Bremen (Germany) for their assistance in the performance of morphologic and biochemical studies.

References

[1] Medina V, Cricco G, Nunes M, Martin G, Mochamad N, Correa-Fiz F, et al. Histamine-mediated signaling processes in human malignant mammary cells. Cancer Biol Ther 2006;5:1462-71.
[2] Davio C, Baldi A, Mladovan A, Gricco G, Fitzsimons C, Bergoc R, et al. Expression of histamine receptors in different cell lines derived from mammary gland and human breast carcinomas. Inflamm Res 1995;44(Suppl 1):S70-1.
[3] Reynolds IL, Akhter JA, Magarey CJ, Schwartz P, Adams WJ, Morris DL. Histamine in human breast cancer. Br J Surg 1998;85:538-41.
[4] Mathes RW, Malone KE, Daling JR, Porter PL, Li CI. Relationship between histamine 2-receptor antagonist medications and risk of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2008;17:67-72.
[5] Garcia-Caballero M, Neugebauer E, Rodrigues F, Nuriez de Castro I, Vara-Thorbeck C. Histamine synthesis and content in benign and malignant breast tumours. Its effects on other host tissues. Surg Oncol 1994;3:167-73.
[6] Taylor KM, Snyder SH. Isotopic microassay of histamine, histidine, histidine decarboxylase and histamine methyltransferase in brain tissue. J Neurochem 1972;19:1343-58.
[7] Watanaba T. Increase in histidine decarboxylase activity in mouse skin after application of the tumor promoter tetradecanoylphrobol acetate. Biochem Biophys Res Commun 1981;100:427-31.
[8] Fogel WA, Ulatowska M, Adach K, Osińska Z. A sum of 14C-putrescine metabolites as a measure of DAO activity. Column chromatography assay. Agents Actions 1985;16:99-101.
[9] Snyder SH, Axelrod J. Sex differences and hormonal control of histamine methyltransferase activity. Biochem Biophys Acta 1965;111:416-21.
[10] Søndergaard I. Quantitative determination of 1,4-methyl-imidazoleacetic acid in urine by high performance liquid chromatography. Allergy 1982;37:581-6.
[11] Stanosz S, von Mach-Szczypiński J, Olewniczak S, Stanosz M. Concentration of histamine in plasma and tissues of the primary ductal breast cancers in women. The Breast 2005;14:236-41.
[12] Nishibori M, Tahara A, Sawada K, Sakiyama J, Nakaya N, Saeki K. Neuronal and vascular localization of histamine *N*-methyltransferase in the bovine central nervous system. Eur J Neurosci 2000;12:415-24.
[13] Sakurai E, Sakurai E, Tanaka Y, Watanabe T, Singh Jossan S, Oreland L. Effects of histamine H3-receptor ligands on brain monoamine oxidase in various mammalian species. Brain Res 2001;906:180-3.
[14] della Rovere F, Granata A, Familiari DA, Arrigo G, Mondello B, Basile G. Mast cells in invasive ductal breast cancer: different behavior in high and minimum hormone-receptive cancers. Anticancer Res 2007;27:2465-71.
[15] Bowrey PF, King J, Magarey C, Schwartz P, Marr P, Bolton E, et al. Histamine, mast cells and tumor cell proliferation in breast cancer: does preoperative cimetidine administration have an effect? Br J Cancer 2000;82:167-70.
[16] Torrisi R, Bagnardi V, Prunesi G, Shisini R. Antitumor and biological effects of letrozole and GnRH analogue as primary therapy in premenopausal women with ER and PgR positive locally advanced operable breast cancer. Br J Cancer 2007;97:802-9.
[17] Rajput AB, Turbin DA, Cheang MCU, Voduc DK, Leng S, Gelmon KA, et al. Stromal mast cells in invasive breast cancer are a marker of favourable prognosis: a study of 4.444 cases. Breast Cancer Res Treat 2008;107:249-57.