HORMONE RECEPTORS IN DYSTROPHIC AND NEOPLASTIC VULVAR DISEASE

Preliminary considerations

L. BECAGLI (*), F. SCRIMIN (*),
D. DE SALVIA (*), M. GAMBATO (*),
P. RESTA (*), A. AMBROSINI (**)

(*) Department of Obstetrics and Gynecology University of Padua (Italy)

(**) Department of Obstetrics and Gynecology University of Sassari (Italy)

SUMMARY

Hormone receptor assays for testosterone, estrogens and androgens were performed on 53 biopsy specimens of vulva from 40 patients, consisting of 6 with normal tissue, 14 with atrophic type dystrophy, 13 with hypertrophic type dystrophy, and 20 with malignancy.

Atrophic and hypertrophic forms showed a different receptor pattern; hypertrophic forms were characterized by consistently higher levels of progesterone receptors not correlated with estrogen receptors.

Neoplastic tissue showed no significant changes in values compared to normal or dystrophic forms, but range of variability was high. The bond between neoplastic forms and hormone activity seems without doubt less important than in the corresponding endometrial and mammary forms. The study of dystrophic forms, instead, should be further explored with a larger number of cases.

In examining the problems related to vulvar disease, the type of bond between vulvar tissue and the steroid sex hormone pattern in women has not yet been clearly explained. On one hand, this tissue is not as directly hormone-dependent as breast or endometrial tissue, but on the other, it is remarkably changed by hormone modifying situations, such as puberty, pregnancy, and menopause. For example, it is known that vulvar dystrophy is a typical menopausal pathology but many workers have described pictures of vulvar dystrophy that begin or become acute again with pregnancy to then disappear or regress at term. Our clinical experience also confirms this finding.

The fact that dystrophic situations often gain benefit from testosterone therapy reproposes the problem. In addition, what bond connects these dystrophic pictures to vulvar carcinoma? Are hormone receptors also present in the neoplastic cells of vulvar tissue? An answer to these questions might help in also clarifying the prognosis in some dystrophic forms regarding their possible evolution into carcinoma, as well as furnish more specific therapeutic approaches.

The bond between tissue and hormone must be studied in depth. As is known ([1-3]), steroids act in target tissues and organs by means of a "receptor" mechanism; in order to explicate their action, it is necessary that a specific bond occurs between the steroid and specific cytoplasm proteins, the receptors, which enables the steroid to act on specific DNA sites following a change in its structure (activation) ([4]). Free steroid, therefore does not raise a biological response, but the same situation, however, may occur due to an alteration or a deficit in the multistep specific mechanism outlined above. Hence, this resistence may take place in the absence of hormone receptors as well as in their presence of the steps following the bond are altered ([1]). Some workers suggest ([1]) the existence of a functional cor-

relation, even if rough, between the quantity of receptor sites and the biological effect of the hormone ([1]). In the case of the genital system, the relative receptor levels of the several interrelated sex hormones must also be considered.

Milgran and co-workers ([5]) previously demonstrated a fluctuation in the concentration of endometrial progesterone receptor sites during the different phases of the sexual cycle. Progesterone ([6]) may inhibit the synthesis of estrogen receptors; estradiol is capable of modulating its own receptor in the uterus. Modifications in the contents of the receptors in various organs during development and senescence have been described ([7]).

All these studies furnish intriguing hypotheses regarding vulval dystrophic disease. The demonstration that the entity of the bond between hormone and receptor might also depend on the metabolic state of the cell is equally interesting; the abolishment of the cortisol bond in thymocytes cultured in the absence of glucose or under anaerobic conditions has been reported ([8]). Finally, it should be ascertained if there is a significant receptor level difference in neoplastic vulval tissue that could be utilized for diagnostic and therapeutic objectives, as occurs presently for other neoplasias. In view of these considerations, we initiated this study in order to evaluate the receptor pattern of normal vulvar tissue and its modifications, if any, with the age of the patient, and ascertain if there is a quantitative and qualitative difference in the receptors (for estrogens, progesterone, and androgen) in vulva with atrophic and hyperthophic dystrophy, and/or neoplasia.

MATERIAL AND METHODS

53 biopsy specimens of vulvar tissue were obtained from 40 patients ranging in age from 28 to 82 years. Due to the fact that vulvar pathology is mucy more frequent in elderly women, as well as the obvious difficulty in obtaining biopsies from healthy women, fertile-age patients were much less numerous than climateric women (8 out of 40).

Receptor levels for estrogens, progesterone and androgen were determined in all the 53 specimens, as well as histological examination, which enabled a comparison between the receptor pattern itself, and the type of pathology present (atrophic, hypertrophic dystrophy, and neoplasia). On histology, we observed 6 normal tissues, 14 atrophic type dystrophies, 13 hypertrophic dystrophies, and 20 neoplasias; five dystrophic forms were associated with carcinoma.

We employed the dextran-coated charcoal method (DCC), which is the most widely used for the determination of estradiol and progesterone receptors in mammary and uterine cancer tissues. The method was standardized under the control of the Italian Committee for the study of neoplastic cell steroid receptors ([9]).

RESULTS

The quantity of receptor sites for estrogens, progesterone and androgens in the vulva is not the same as generally found in endometrial or breast tissue, and the values we obtained were decidedly lower; in the six cases of histologically normal tissue, estrogen receptors ranged from 0 to 20.9 pg/ml, progesterone receptors from 0 to 24.7, and androgen receptors from 0 to 27.7. Similar results were obtained in tissues with dystrophy or neoplasia.

The level of progesterone receptors is significantly and consistently high, in contrast with reports for other tissues and organs in the literature, which considers the progesterone receptors the result of an estrogen receptor-mediated activity. In other words, progesterone receptor has been described as one of the final effects of the interaction between estrogens and target cell, and requires, therefore, the integrity of the estrogen receptor mechanism at the start of the process leading to the hormone response ([10, 11]). The significance of its stability independently of estrogen receptor in vulvar tissue has yet to be evaluated. The receptor pattern in our case series does not tend to change with the patients age, but this finding may

be biased by the very small number of young, fertile women ([7]).

The dystrophic pictures commanded our greatest attention, as we were particularly interested in understanding if the good results obtained with some hormone therapies ([12]), for example testoserone, corresponded to a specific receptor pattern in the several dystrophic forms. In particular, we looked for a correlation between the levels of the three receptors and their changes in the several pathological forms.

In 14 cases of atrophic type dystrophy, there was no correlation between levels of estrogen and androgen receptors, nor between androgens and progesterone; it was very low (index 0.69) between progesterone and estrogen receptors. The overall level of the three receptors in these atrophic forms was positive, that is, biologically significant in 8 cases out of 14. The variations in the levels were rather high; estrogen receptors ranged from 0 to 55.2 pg/ml, progesterone from 0 to 34, and androgens form 0 to 1952.

In reference to the 13 cases of hypertrophic dystrophy, no correlation between the three receptors emerged, except for a very low correlation between estrogen and androgen receptors (index, 0.67).

Only one case out of 13 presented receptor levels that had a positive biological significance. This finding might differentiate the atrophic from the hypertrophic form. In addition, the hypertrophic forms might be characterized by a constantly higher level of progesterone receptors, with were over 10 pg/ml in 9 cases out of 13, with no apparent correlation with estrogen receptors.

We also attempted establish if the correlations between the receptors could modify with the site of biopsy, which in some cases was obtained in the great lips, in others, the small lips, clitoral or perineal zone. Unfortunately, normal cases were too few in number to elaborate a map of the receptor level in the various districts, that presumably are different. We therefore examined the pothological cases, and limited the study of the various correlations respectively in the atrophic and hypertrophic tissues biopsied only in the great lips. 8 cases of atrophic forms were biopsied at this site, and no correlation emerged among the three receptors. 9 cases of hypertrophic forms were biopsied in the great lips, and again no correlation emerged. The findings therefore apparently do not change with site, even if it is possible that disease might have altered normal relationships.

Concerning the 20 cases of carcinoma, there was no significant change compared to values in normal or dystrophic tissue. Levels were regularly low; a true positivity, that is, the presence of significant levels in consideration of the sensitivity of the method used, was seen only in 4 cases, and two were weakly positive.

The range of variability was rather high, from 0 to 135 for estrogens, 0 to 74 for progesterone, and 0 to 21.7 for androgens. A study of the correlations among the different receptors shows a relationship between estrogen and progesterone receptors with an index of 0.94, estrogen and androgen receptors with an index of 0.81, and androgen and progesterone receptors with an index of 0.72. In limiting the carcinoma cases to the 11 forms that arose only in the great lips, the correlation index does not change greatly; between estrogen and androgens, it is 0.89, progesterone and androgens, 0.81, and progesterone and estrogens, 0.76. In addition, the neoplastic forms do not show that greater stable presence of progesterone receptors that was found in normal or dystrophic tissues.

Patients under topical testosterone treatment at the moment of this investigation (5 cases) did not present striking modifications in androgen receptor levels, compared to normal levels; the only interesting finding consisted of the fact that the

Table 1.

Patient	No.	Age	E.R.	P.R.	A.R.	Histological diagnosis	
C. A.	1	74	10.2	6.02	4.4	Carcinoma	
S. M.	2	67	2.9	0.24	—	»	
D. M.	3	73	6.4	9.3	—	»	
S. A.	4	77	21.4	12.0	12.7	»	
C. F.	5	58	135.0	74.0	21.7	»	
D. S.	6	49	—	3.9	0.21	»	
M. E.	7	43	8.4	1.6	2.7	»	
B. M.	8	79	5.6	—	1.3	»	
M. L.	9	64	1.7	—	—	»	
B. M.	10	73	—	—	1.4	»	
T. D.	11	65	—	17.9	—	»	
F. M.	12	49	—	24.3	—	»	
S. A.	13	62	17.1	7.9	—	»	
U. P.	14	70	3.9	7.0	1.6	»	
P. M.	15	60	11.2	1.03	2.02	»	
M. G.	16	58	49.5	19.6	21.6	»	
R. A.	17	76	2.7	8.0	9.3	»	
F. L.	18	54	3.1	11.2	—	»	
A. L.	19	63	1.4	4.0	—	»	
F. M.	20	38	4.4	3.1	2.5	Paget's disease	
V. A.	21	64	24.7	15.1	9.4	Hypertrophic dystrophy	
V. G.	22	55	—	42.6	0.74	»	
P. L.	23	82	7.1	16.3	10.4	»	
M. G.	24	70	—	14.0	—	»	
M. P.	25	62	—	22.0	—	»	
S. M.	26	28	4.1	15.8	3.0	»	
C. L.	27	69	—	11.9	8.5	»	
A. F.	28	45	—	7.2	—	»	
B. L.	29	68	—	22.3	—	»	
F. C.	30	60	—	8.4	0.98	»	
D. M.	3	73	—	12.6	—	»	(1)
S. A.	4	77	—	3.9	0.2	»	(1)
M. E.	7	43	2.2	3.4	3.2	»	(1)
Z. E.	31	44	36.3	33.4	—	Atrophic dystrophy	
S. M.	32	55	16.4	23.2	—	»	
P. A.	33	72	0.56	3.7	3.1	»	
B. V.	34	54	—	21.4	—	»	
M. S.	35	67	14.2	15.7	19.2	»	
C. L.	36	69	1.5	11.5	—	»	
B. F.	37	45	—	15.9	—	»	
C. A.	38	69	39.0	19.3	18.1	»	
L. P.	39	63	33.8	22.6	—	»	
T. M.	40	72	55.2	34.0	15.7	»	
U. P.	14	70	20.4	6.9	13.1	»	(1)
R. A.	17	76	6.7	—	5.6	»	(1)
C. L.	27	69	14.2	18.7	1.3	»	(2)
A. F.	28	45	—	20.3	—	»	(2)
S. M.	26	28	10.4	6.5	8.4	Normal tissue	(2)
F. C.	30	60	9.6	7.2	6.9	»	(2)
S. M.	32	55	20.9	12.7	18.6	»	(3)
B. V.	34	54	—	24.7	22.0	»	(3)
B. F.	37	45	1.14	—	—	»	(3)
T. M.	40	72	16.0	15.3	27.7	»	(3)

(1): in patient with carcinoma too
(2): in patient with hypertrophic dystrophy too
(3): in patient with atrophic dystrophy too

quantity of androgen receptors in these cases is remarkably higher compared to the corresponding estrogen and progesterone receptors. We may suggest a greater sensitivity to testosterone therapy due to a greater presence of receptors in these cases ([13]), and inversely, the presence of the hormone induces its receptor.

CONCLUSIONS

The wide variability in receptor levels found in the biopsies of vulvar tissue in this limited case study led us to formulate only a few working hypotheses. The role played by hormone therapies, especially in dystrophic situations of menopause and old age, constitutes a still open problem, which we intend to study in depth with a larger patient sample including normal and pothologic tissue. The few reports ([14]) available in this regard do not permit a comparison of case series.

In our opinion, further study should be given to the hypothesis of a different receptor pattern in dystrophic forms (our series shows a different receptor level in the atrophic compared to the hypertrophic forms), or the possible presence of a local mechanism of resistance to the action of the hormones themselves. The prospects of such a study are interesting because of the etiopathogenetic and therapeutic implications involved. In reference to the neoplastic forms, the bond with hormone activity seems without doubtless important than in the corresponding endometrial and mammary forms.

BIBLIOGRAPHY

1) Natoli C., Zenobi R.: *Meccanismi della resistenza all'azione degli ormoni steroidei.* In: Iacobelli S.: *Ormoni, recettori e cancro,* Società editrice Universo, Roma, 1979.
2) Baulieu E. E.: *Biochem. Pharmacol., 24,* 1743, 1975.
3) Higgins S. J., Ghering U.: *Adv. Cancer Res., 28,* 313, 1978.
4) Schimke R. T., Mcknight G. S., Shapiro D. J., Sullivan D., Palacios R.: *Recent Prog. Horm. Res., 31,* 175, 1975.
5) Milgron E., Luu Thi M., Baulieu E. E.: *Control mechanisms of steroid hormone receptors in the reproductive tract.* In: *Karolinska symposia on research methods in reproductive endocrinology.* Sixth Symposium: *Protein synthesis in reproductive tissue,* p. 380, 1973.
6) Hsueu A. J. W., Pecky E. J., Clark J. H.: *Endocrinology, 98,* 438, 1976.
7) Giannopoulos G., Hasson Z., Solomon S.: *J. Biol. Chem., 249,* 2424, 1974.
8) Ramelletti F. O., Natoli C., Jacobelli S.: *Ormoni, recettori, crescita differenziale e cancro.* In: Iacobelli S.: *Ormoni recettori e cancro,* Società editrice Universo, Roma, 1979.
9) Piffanelli A., Fumero S., Pelizzola D., Berruto G. P., Ricci L., Giovannini G.: *LAB - Giorn. Ric. Diagn. Lab., 772,* 1, 1981.
10) Baulieu E. E.,: *Steroid receptors and hormone receptivity: new approaches in pharmacology and therapeutics.* In: Straub R.W., Bolis L.: *Cell membrane receptors for drugs and hormones a multidisciplinary approach.* New York, Raven Press, p. 129, 1978.
11) Ros A., Cappelletto T.: *I recettori ormonali nel carcinoma della mammella e dell'endometrio.* Ed. Libreria Cortina, Verona, 1981.
12) Ambrosini A., Becagli L., Scrimin F., De Salvia D., Resta P., Gambato M.: *Topical testosterone propionate in the therapy of vulvar dystrophies.* (In print).
13) Nenji Adachi: *J. Invest. Dermat., 62,* 217, 1974.
14) Johansson R., Gronross M., Kouvonen I., Lovgren T.: *Acta Obst. Gyn. Scand., 58,* 213, 1979.