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IV. Peptide Hormones and Cancer

BIOLOGICAL AND CLINICAL ASPECTS OF PROLACTIN RECEPTORS (PRL-R) IN HUMAN BREAST CANCER

J. BONNETERRE, J. P. PEYRAT, R. BEUSCART and A. DEMAILLE
Centre Oscar Lambret, 1 rue F. Combemale, BP 307, 59020 Lille Cédex, France

Summary—PRL has a definite activity in the induction and promotion of mouse and in the growth of rat mammary tumors. We and others have found that human PRL or growth hormone (GH) had a growth promoting effect on human mammary cancer cells. It has been shown that prolactin receptors (PRL-R) which are specific for all lactogenic hormones (hPRL, hGH, hPL) are present on mammary cancer cells in long-term tissue culture and also in tumor biopsies. We found that 43% of the tumors had free PRL-R (FPRL-R) and that 72% had total PRL-R (TPRL-R) which have been desaturated *in vitro*. A significant correlation (Spearman test) was found between PRL-R (especially TPRL-R) on the one hand, estradiol ($P < 0.001$) and progesterone receptors ($P < 0.01$) on the other. The demonstration of PRL-induced proteins (PIP) might be a better sign of PRL sensitivity than the existence or PRL-R; PIP have been found by Northern blot analysis in 47% of 70 breast cancers. Overall survival (OS) and relapse-free survival (RFS) analysis with a median duration of follow-up of 5.3 yr showed that TPRL-R had a significant prognostic value only in node positive patients ($\chi^2 = 5.61$, $P = 0.02$). Neither FPRL-R or TPRL-R were a significant prognostic factor when studied by Cox analysis. This confirms our previous results. Since at least some human mammary cancers appear to be PRL-dependent we carried out a multicenter randomized trial comparing as the first hormonal treatment tamoxifen (TAM) (30 mg/day) + bromocriptin (B) (5 mg/day) vs TAM + placebo. 171 patients entered this trial. No difference was observed between the two groups in response rates, duration of response or survival.

Recent studies are thus in favor of a role of lactogenic hormones during the course of breast cancer. However no improvement in therapy has been observed yet. The combination of drugs to achieve a total anti-lactogenic treatment, the use of anti-PRL-R antibodies are interesting areas of research; the recent cloning of PRL-R and GH receptors may open new clinical perspectives.

INTRODUCTION

Prolactin (PRL) plasma levels and PRL-R have been the subject of many publications for the last 20 yr. The precise role of PRL in the genesis and/or the growth of breast cancer as well as the significance of high PRL plasma levels during or after treatment is not clear. However, some new insights in the biology of PRL-R allow a better understanding of some aspects of the role of PRL. Furthermore recent results such as the cloning of the human PRL-R gene provide new tools which will probably stimulate further research [1].

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BIOLOGICAL ASPECTS

Characterization of PRL-R

PRL-R have been shown to have in human breast cancer a dissociation constant (K_d) of about 10^{-10} M [2]. Similar results had been previously obtained in long-term tissue culture by Shiu [3] and Murphy *et al.* [4]; competition studies showed that all lactogenic hormones in man could bind to PRL-R: human (h) PRL but also hGH, human placental lactogen (hPL) and to a lesser degree ovine PRL. Covalent linking of labeled hPRL to PRL-R and subsequent sodium dodecyl sulfate–polyacrylamide gel electrophoresis demonstrated one major band with a relative molecular weight of 36,700 as described previously in a normal mammary gland.

High PRL plasma levels are generally observed immediately before surgery for breast

Table 1. PRL-R-induced breast cancer cell proliferation

Salih *et al.* [37]	Tumor explant	+
Beedy *et al.* [38]	Tumor explant	0
Masters *et al.* [39]	Tumor explant	+
Welsh *et al.* [40]	Tumor explant	+
Klevjer-Anderson and Case-Buehring [41]	Primary culture	+
Malarkey *et al.* [42]	Primary culture	+
Simon *et al.* [14]	Primary culture	+
Manni *et al.* [15]	Clonogenic assay	+
Shafie and Brooks [43]	MCF-7	0
Leung and Shiu [44]	T47-D	+
Shiu and Paterson	MCF-7	0
Biswas and Vonderhaar [11]	MCF-7	+

cancer; PRL might thus saturate the tumor PRL-R. We used $MgCl_2$ desaturation *in vitro* [5]; the desaturation was maximal at 3 M; this treatment did not denaturate PRL-R since rebinding with human PRL was possible. A protein loss of about 30% was observed during this procedure. These desaturated receptors were called total PRL-R (T-PRL-R); the non-desaturated ones free PRL-R (F-PRL-R).

Regulation of PRL-R

PRL induces a short-term down-regulation and a long-term up-regulation in the rat liver as well as in rabbit mammary gland [6]. In T47-D cells PRL-R down-regulation was obtained only with very high concentrations of GH (more than 500 ng/ml); R-5020, a synthetic progestin, induced a significant increase in PRL-R whereas estradiol, cortisol, dexamethasone and RU 486 (a progestin and glucocorticoïd antagonist) had no effect [7]. These results are in agreement with those of Murphy *et al.* [8] on the same cell line. Simon *et al.* [9] using EFM 19 line found an up- and down-regulation of PRL-R by homologous hormone as well as modulations with estradiol and dihydrotestosterone.

Growth promoting effect of PRL (Table 1)

The early results concerning the growth promoting effects of PRL were conflicting probably due to the quality and the concentration of the hormone used [10], and, in long-term tissue culture, to the interaction of bovine PRL (found in fetal calf serum) with PRL-R [11]. We found a stimulation of thymidine uptake in tumor explants with ovine PRL concentrations of 50–200 ng/ml. The stimulation was observed in PRL-R-positive tumors but not in all of them [12]. Such a stimulation has been repeatedly found either in cell lines [13] or in primary culture using different biological methods [14, 15].

Prolactin-induced proteins (PIP)

Shiu *et al.* [16] described three immunologically similar PIP with respective molecular weight of 11, 14 and 16 K in T47-D cells. Treatment of T47-D cells with HGH increased PIP mRNA levels by 4.6-fold, whereas the combination HGH-hydrocortisone or dihydrotestosterone had a more dramatic 12.4-fold effect. Some PRL-R positive cell lines (MCF-7, EFM 19) did not express PIP. PIP mRNA was studied in 70 human breast cancers; 47% were positive.

Cloning of PRL-R or PIP genes

The rat liver PRL-R gene has recently been cloned [1] as well as the GH-R gene from rabbit and human liver [17]. More recently Boutin *et al.* [1] cloned the PRL-R gene of human breast cancer cells. PIP gene has also been cloned [16].

In mouse liver, PRL-R mRNAs appear to be encoded by at least two genes suggesting the existence of multiple PRL-R with possibly different modulation or activity [19].

CLINICAL ASPECTS

PRL-R determination in human breast cancer

Since the first study of Holdaway and Friesen [20], several groups have published their results summarized in Table 2. The technique used is very similar in all the studies, derived from Shiu's [3]. Overall positivity rates are about 40% (mostly between 30 and 50%). Differences may be due to the type and quality of the radioligand and the quality of the membrane preparation. hPRL and hGH appear to be the best ligands; in our hands (unpublished results) the positivity rate of PRL-R when using oPRL was 20%,

Table 2. PRL-R determination in human breast cancer

	n	Radio-ligand	+ Rate (%)
Holdaway and Friesen [20]	41	HPRL	20
Pearson *et al.* [46]	111	oPRL	51
Di Carlo and Muccioli [47]	238	HPRL	43
Partridge and Hähnel [24]	8	oPRL	37.5
Bohnet [48]	24	HPRL	30
		HGH	8
Rae Venter *et al.* [26]	55	HPRL	58
Turcot-Lemay and Kelly [49]	759	HPRL	36
		oPRL	13
		HGH	2
Murphy *et al.* [25]	31	HGH	65
Waseda *et al.* [27]	214	HGH	13
Ben David *et al.* [28]	>300	HPRL	42
Bonneterre *et al.* [23]	547	HGH	43 (free) 72 (total)
L'Hermite-Baleriaux *et al.* [21]	199	oPRL	19

very close to the 19% obtained by l'Hermitte-Baleriaux *et al.* [21]. To our knowledge no other group published results on T-PRL-R determination: our positivity rate was 72% in 395 patients. It is interesting to note that using immunohistochemistry, Dhadly and Walker [22] observed a 56% positivity rate and that Shiu *et al.* [16], by Northern blot analysis observed PIP mRNA in 47% of the tumors.

Correlation between PRL-R and ER, PgR

The distribution of F-PRL-R was not different in ER+ and ER− patients (respectively 45 and 36%) (NS); conversely T-PRL-R were more often found in ER+ than in ER− patients (respectively 75 and 63%) ($P < 0.03$). By the Spearman test a correlation was found between F-PRL-R and ER ($P = 0.02$) and PgR ($P = 0.05$); between T-PRL-R and ER ($P < 0.001$), PgR ($P < 0.001$) [23]. Such a relation had been suggested by Holdaway and Friesen [20], Partridge and Hähnel [24], Murphy *et al.* [25]. Rae-Venter *et al.* [26] found no correlation but tumors between 6 and 100 fmol/mg of ER had higher levels of PRL-R; the absence of correlation could be due to low PRL-R in patients with very high ER. Waseda *et al.* [27] did not find a correlation either but the positivity rates of PRL-R (15%), ER (47%) and PgR (36%) were very different of the ones observed by other groups. Finally Ben David *et al.* [28] reported a lack of correlation between the levels of PRL-R and those of ER or PgR; however the difference in PRL-R positivity rates between ER+ and ER− patients was of borderline significance and the difference between ER+, PgR+ and ER−, PgR− was significant; no Spearman test was carried out. Thus it appears difficult to rule out a relation between these receptors. In our hands the difference between ER+ and ER− tumors was significant only for T-PRL-R. It is worth noting that Shiu *et al.* [16] observed PIPs only in ER+ cell lines.

Prognostic significance

We published results on the prognostic significance of T-PRL-R on the relapse-free survival of patients with locoregional breast cancer [29]; the difference was significant in actuarial survival analysis but not in Cox analysis. The results have been updated with a median follow-up time over 5 yr. T-PRL-R still have a prognostic significance on relapse-free survival of patients with axillary node metastases ($P < 0.02$). No prognostic value was observed left in all the patients ($P = 0.18$) and in ER+ ones ($P = 0.08$). This prognostic significance was thus limited to the first years of follow-up. The Cox analysis was negative too. To our knowledge, only Waseda *et al.* [27] studied the prognostic significance of PRL-R; these receptors could be markers of a poor prognosis; again the positivity rate of PRL-R must be taken into account before interpreting these results which—to our knowledge—have never been confirmed.

Anti-prolactinic treatment

Lactogenic hormones can have a growth promoting action at least on some breast cancer cells; a treatment which aims at lowering lactogenic hormones could thus limit the growth of the tumor. However, bromocriptin, a PRL lowering drug, was found to be ineffective in a phase II trial of the EORTC [30].

Experimental data show that the growth inhibition of CGS cell line was more important when using tamoxifen and bromocriptin than either drug alone [31]. This suggests a possible direct action of bromocriptin at the cancer cell level. More recently, it has been suggested that anti-estrogens can inhibit the binding of lactogenic hormones on their receptors at least on the NB2 rat lymphoma cell line [13].

We carried out a multicenter double blind randomized trial comparing tamoxifen + bromocriptin to tamoxifen + placebo as first hormonal treatment in advanced breast cancer patients. 171 patients entered this study—151 were evaluable for efficacy. No difference was observed in response rates between the two groups. The tolerability was good in the two groups [32]. The absence of benefit could be explained by the absence of total antilactogenic treatment; it is clear that bromocriptin has no effect on normal GH secretion; it is not known whether a 5 mg/day bromocriptin treatment is adequate for a "total" 24 h a day inhibition of secretion of PRL in normoprolactinemic patients. An interaction between tamoxifen and bromocriptin or their receptors appears to be unlikely; tamoxifen treatment does not induce hyperprolactinemia; experimentally it has no effect on PRL sensitivity of cells (at least after 24 h) [33]; ER positivity after bromocriptin treatment was not lower than in the control population [34]. F-PRL-R as well as T-PRL-R were not different in bromocriptin treated and untreated patients which suggests that in cancer cells PRL-R are no longer regulated by PRL plasma levels; last but

not least, the PRL-R status of the patients was not known.

Robustelli Della Cuna *et al.* [35] published the results of a similar study using higher bromocriptin dose (10 mg) and medroxyprogesterone acetate (1 g × 30 days and then 500 mg/day). No difference was observed between the bromocriptin treated patients and the untreated ones.

Fentiman *et al.* [36] compared the S-phase of 18 tumors of patients treated with bromocriptin 5 days pre-operatively to the one of 20 tumors from untreated patients. A significant difference in S-phase fraction of the tumors was observed, the lower one being obtained in bromocriptin treated patients. This confirms the effect of PRL on breast cancer growth.

CONCLUSION

Lactogenic hormones are growth-simulatory for at least some breast cancers. The regulation of PRL-R is complex and several lines of evidence suggest that it may be impaired in cancer cells. The cloning of PRL-R genes will provide new tools to better understand the biology of PRL-R. From the therapeutic point of view results obtained so far are disappointing. The combination of antiprolactinic and anti-GH drugs (like somatostatin) could possibly have an antitumour action—and would surely provide new insights in the biology of the PRL sensitivity of human breast cancer.

REFERENCES

1. Boutin J. M., Edery M., Shitora C., Jolicoeur C., Lesueur L., Ali S., Gould D., Djiane J. and Kelly P. A.: Identification of cDNA encoding a long form of prolactin receptor in human hepatoma and breast cancer cells. *Molec. Endocr.* **3** (1989) 1455–1461.
2. Peyrat J. P., Djiane J., Kelly P. A., Vandewalle B., Bonneterre J. and Demaille A.: Characterization of prolactin receptors in human breast cancer. *Breast Cancer Res. Treat.* **4** (1984) 275–281.
3. Shiu R. P. C.: Prolactin receptors in human breast cancer cells in long-term tissue culture. *Cancer Res.* **39** (1979) 4381–4386.
4. Murphy L. J., Vrhosek E., Sutherland R. L. and Lazarus L.: Growth hormone binding to cultured human breast cancer cells. *J. Clin. Metab.* **58** (1984) 149–156.
5. Peyrat J. P., Dewailly D., Djiane J., Kelly P. A., Vandewalle B., Bonneterre J. and Lefebvre J.: Total prolactin binding sites in human breast cancer biopsies. *Breast Cancer Res. Treat.* **1** (1981) 369–373.
6. Kelly P. A., Djiane J., Katoh M., Ferland J. M., Houdebine L. M., Teyssot B. and Dusanter-Fourt I.: The interaction of prolactin with its receptors in target tissues and its mechanism of action. *Recent Prog. Horm. Res.* **40** (1984) 379–439.
7. Leroy-Martin B. and Peyrat J. P.: Modulation of prolactin receptors (PRL-R) by lactogenic and steroid hormones in human breast cancer cells in long-term tissue culture (T47-D). *Anticancer Res.* **9** (1989) 631–636.
8. Murphy L. J., Sutherland R. L. and Lazarus L.: Regulation of growth hormone and Epidermal growth factor receptors by progestins in breast cancer cells. *Biochem. Biophys. Res. Commun.* **131** (1985) 767–773.
9. Simon W. E., Pahnke V. G. and Holzel F.: *In vitro* modulation of prolactin binding to human mammary carcinoma cells by steroid hormones and prolactin. *J. Clin. Endocr. Metab.* **60** (1985) 1243–1249.
10. Bonneterre J., Peyrat J. P. and Demaille A.: Prolactin (PRL) and breast cancer. An update. *Breast Dis. Senol.* **1** (1985) 3–26.
11. Biswas R. and Vonderhaar B. K.: Role of serum in the prolactin responsiveness of MCF-7 human breast cancer cells in long-term tissue culture. *Cancer Res.* **47** (1987) 3509–3514.
12. Peyrat J. P., Djiane J. and Bonneterre J.: Stimulation of DNA synthesis by prolactin in human breast tumor explants. Relation to prolactin receptors. *Anticancer Res.* **4** (1984) 275–281.
13. Biswas R. and Vonderhaar B. K.: Anti-estrogen inhibition of prolactin induced growth of the Nb2 rat lymphoma cell line. *Cancer Res.* **49** (1989) 6295–6299.
14. Simon W. E., Albrecht M. and Trams G.: *In vitro* growth promotion of human mammary carcinoma cells by steroid hormones, tamoxifen and prolactin. *J. Natn. Cancer Inst.* **73** (1984) 313–321.
15. Manni A., Wright C., Davis g., Glenn J., Joehl R. and Feil P.: Promotion by prolactin of the growth of human breast neoplasms cultured *in vitro* in the soft agar clonogenic assay. *Cancer Res.* **46** (1986) 1669–1672.
16. Shiu R. P. C., Murphy L. C., Tsuyuki D., Myal Y., Lee-Wing M. and Iwasiow B.: Biological actions of prolactin in human breast cancer. *Recent Prog. Horm. Res.* **43** (1987) 277–303.
17. Boutin J. M., Jolicœur C., Okamura H., Gagnon J., Edery M., Shirota M., Banville D., Dusanter-Fourt I., Djiane J. and Kelly P. A.: Cloning and expression of the rat prolactin receptor, a member of the growth hormone/prolactin receptor gene family. *Cell* **53** (1988) 69–77.
18. Leung D. W., Spencer S. A., Cachianes G., Hammonds R. G., Collins C., Henzel W. J., Barnard R., Waters M. J. and Wood W. J.: Growth hormone receptor and serum binding protein: purification, cloning and expression. *Nature* **330** (1988) 537–543.
19. Davis J. A. and Linzer D. I. H.: Expression of multiple forms of the prolactin receptor in mouse liver. *Molec. Endocr.* **3** (1989) 674–680.
20. Holdaway I. M. and Friesen H. G.: Hormone binding by human mammary carcinoma. *Cancer Res.* **37** (1977) 1946–1952.
21. L'Hermite-Baleriaux M., Casteels S. and L'Hermite M.: Prolactin receptors in breast cancer: importance of the membrane preparation. In *Hormonal Manipulation of Cancer* (Edited by J. G. M. Klijn, R. Paridaens and J. A. Foekens). Raven Press, New York (1987) pp. 157–165.
22. Dhadly M. S. and Walker R. A.: The localization of prolactin binding sites in human breast tissue. *Int. J. Cancer* **31** (1983) 433–437.
23. Bonneterre J., Peyrat J. P., Beuscart R. and Demaille A.: Correlation between prolactin receptors (PRL-R) estradiol (ER) and progesterone receptors (PgR) in human breast cancer. *Eur. J. Cancer Clin. Oncol.* **22** (1986) 1331–1336.
24. Partridge R. K. and Hähnel R.: Prolactin receptors in human breast carcinoma. *Cancer* **43** (1979) 643–646.
25. Murphy L. J., Murphy L. C., Vrhousek E., Sutherland R. L. and Lazarus L.: Correlation of lactogenic receptor concentration in human breast cancer with estrogen receptor concentration. *Cancer Res.* **44** (1984) 1963–1968.

26. Rae-Venter B., Nemoto R., Schneider J. L. and Dao T. C.: Prolactin binding by human mammary carcinoma: relationship to estrogen receptor protein concentration and patient age. *Breast Cancer Res. Treat.* **1** (1981) 233–243.
27. Waseda N., Kato Y., Imura H. and Kurata M.: Prognostic value of estrogen and prolactin receptor analysis in human breast cancer. *Jap. J. Cancer Res. (Gann)* **76** (1985) 518–523.
28. Ben-David M., Wittliff J. L., Fekete M., Kadar T., Biran S. and Shally A. V.: Lack of relationship between the levels of prolactin receptors and steroid receptors in women with breast cancer. *Biomed. Pharmacother.* **42** (1988) 327–334.
29. Bonneterre J., Peyrat J. P., Beuscart R., Lefebvre J. and Demaille A.: Prognostic significance of prolactin receptors in human breast cancer. *Cancer Res.* **47** (1987) 4724–4728.
30. European Breast Cancer Group (EORTC): Clinical trial of 2 Br-ergocriptine (CB 154) in advanced breast cancer. *Eur. J. Cancer* **8** (1972) 155–156.
31. Di Carlo F., Muccioli G., Bellussi G., Guibertoni M., Natoli U. and Sica G.: Experimental supports of the possible usefulness of combining hypoprolactinemic drugs with "common" hormonal treatments in human breast cancer. *Anticancer Res.* **6** (1986) 348.
32. Bonneterre J., Mauriac L., Weber B., Roche M., Fargeot P., Tubiana-Hulin M., Sevin M., Chollet P. and Cappelaere P.: Tamoxifen (T) plus bromocriptin (B) vs Tamoxifen plus placebo in advanced breast cancer: results of double blind multicenter trial. *Eur. J. Cancer Clin. Oncol.* **24** (1988) 1851–1853.
33. Natoli U., Muccioli G., Bellussi G., Di Carlo F. and Sica G.: Tamoxifen modifies ^{125}I human prolactin binding in human breast cancer cells. *Anticancer Res.* **6** (1986) 386–397.
34. Peyrat J. P., Vennin Ph., Bonneterre J., Hecquet B., Vandewalle B., Kelly P. A. and Djiane J.: Effect of bromocriptin treatment on prolactin and steroid receptor levels in human breast cancer. *Eur. J. Cancer Clin. Oncol.* **20** (1984) 1363–1367.
35. Robustelli Della Cuna G., Dogliotti L. and Di Carlo F.: High dose medroxyprogesterone acetate (HD-MPA) vs HD-MPA + bromocriptin (BR) in metastatic breast cancer; a randomized multicentric clinical trial. *14th International Cancer Congress*, Budapest (1986). (Abstr. 3391).
36. Fentiman I. S., Brame K., Chaudary M. A., Camplejohn R. S., Wang D. Y. and Millis R. R.: Peri-operative bromocriptine adjuvant treatment for operable breast cancer. *Lancet* **i** (1988) 609–610.
37. Salih H., Flax H. and Brander W.: Prolactin dependence in human breast cancer. *Lancet* **25** (1972) 1103–1104.
38. Beedy D. F., Easty G. C. and Gazet J. C.: An assessment of the effects of hormones on short term organ cultures of human breast carcinoma. *Br. J. Cancer* **31** (1975) 317.
39. Masters J. R. W., Sangster K. and Smith H.: Human breast carcinoma organ cultures: the effect of hormones. *Br. J. Cancer* **33** (1976) 564.
40. Welsh C. Q., De Itturi C. and Brenman M. J.: DNA synthesis of human mouse and rat mammary carcinomas *in vitro*. Influence of insulin and prolactin. *Cancer* **38** (1977) 1272–1282.
41. Klevjer-Anderson P. and Case-Buehring G.: Effects of hormones on growth rates of malignant and non-malignant human mammary epithelium in cell culture. *In Vitro* **16** (1980) 491–501.
42. Malarkey C. V. B., Kennedy M., Allred L. E. and Millo G.: Physiological concentrations of prolactin can promote the growth of human breast tumor cells in culture. *J. Clin. Endocr. Metab.* **56** (1983) 673–677.
43. Shafie J. and Brooks J. C.: Effect of prolactin on growth and the estrogen receptor level of human breast cancer cells (MCF-7). *Cancer Res.* **37** (1977) 792–799.
44. Leung C. K. H. and Shiu P. C.: Required presence of both estrogen and pituitary factors for the growth of human breast cancer cells in athymic nude mice. *Cancer Res.* **41** (1981) 546–551.
45. Shiu R. P. C. and Paterson J. A.: Alteration of cell shape, adhesion and lipid accumulation in human breast cancer cells (T47-D) by human prolactin and growth hormone. *Cancer Res.* **44** (1984) 1178–1186.
46. Pearson O. H., Manni A., Chambers M., Brodkey J. and Marshall J. S.: Role of pituitary hormones in the growth of human breast cancer. *Cancer Res.* **38** (1978) 4323–4326.
47. Di Carlo R. and Muccioli G.: Prolactin receptors in human mammary carcinoma. *Cancer* **43** (1979) 643–646.
48. Bohnet H. G.: Determination and properties of proteohormone receptors in malignant gynecological tumors with special reference to lactogen receptors in human breast cancer. *Arch. Gynec.* **229** (1980) 333–344.
49. Turcot-Lemay L. and Kelly P. A.: Prolactin receptors in human breast tumors. *J. Natn. Cancer Inst.* **68** (1982) 381–383.