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VI. Somatostatin Analogs and Cholecystokinin Inhibitors

ANTITUMOR EFFECTS OF ANALOGS OF LH-RH AND SOMATOSTATIN: EXPERIMENTAL AND CLINICAL STUDIES

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Summary—Many clinical approaches for the treatment of hormone-sensitive tumors are being developed based on analogs of LH-RH and somatostatin. Inhibition of the pituitary–gonadal axis forms the basis for oncological applications of LH-RH agonists like [D-Trp^6]-LH-RH and new LH-RH antagonists free of edematogenic effects such as [Ac-D-Nal(2)^1-D-Phe(4Cl)^2-D-Pal(3)^3,D-Cit^6,D-Ala^{10}]-LH-RH (SB-75). Agonists and antagonists of LH-RH have been used in patients with prostate cancer and might be also beneficial for the treatment of breast cancer and ovarian, endometrial and pancreatic carcinomas. Some of the effects of LH-RH analogs can be due to direct action since LH-RH receptors have been found in these cancers. The use of sustained delivery systems based on microcapsules of PLG, makes the treatment more efficacious. Octapeptide analogs of somatostatin such as D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH_2 (RC-160) and related analogs were designed specifically for antitumor activity. These somatostatin analogs, by virtue of having a wide spectrum of activities appear to inhibit various tumors through multiple mechanisms. Direct antiproliferative actions of somatostatin analogs appear to be mediated by specific receptors located on tumor cells. High affinity binding sites for RC-160 and related analogs have been found in human pancreatic, prostate, breast and ovarian cancers and brain tumors such as meningiomas. *In vivo* administration of analog RC-160 inhibits the growth of Dunning R-3327 prostate cancers in rats, MXT mammary tumors in mice and BOP-induced ductal pancreatic cancers in hamsters. Combination of microcapsules of RC-160 with [D-Trp^6]-LH-RH results in synergistic potentiation of the inhibition of these cancers. Somatostatin analog RC-160 and LH-RH antagonist SB-75 are the object of further experimental studies and clinical trials aimed at the exploration of their inhibitory effects on the processes of malignant growth.

INTRODUCTION

In this article we will summarize recent studies with analogs of LH-RH and somatostatin carried out by our group in various models of endocrine-dependent or hormone-sensitive tumors. The development of new classes of antitumor peptides based on LH-RH analogs carrying various cytotoxic radicals and of bombesin/GRP receptor antagonists will be also mentioned. Clinical trials with analogs of LH-RH and somatostatin on specific neoplasms will be briefly cited. This article will focus on inhibitory effects of peptide analogs on various tumors *in vivo* and *in vitro* and on membrane peptide receptors found in many cancers. There

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Abbreviations: BOP, *N*-nitrosobis(2-oxopropyl)amine; CCK, cholecystokinin; Cit, citrulline (2-amino-5-ureidopentanoic acid); EGF, epidermal growth factor; FSH, follicle-stimulating hormone; GH, growth hormone; G.I., gastrointestinal; GRP, gastrin releasing peptide; Hci, homocitrulline (2-amino-6-ureidohexanoic acid; IGF-I, insulin-like growth factor I or somatomedin C; LH, luteinizing hormone; LH-RH, luteinizing hormone-releasing hormone; Nal(2), 3-(2-naphthyl)-alanine; Orn, ornithine (2,5-diaminopentanoic acid); Pal(3), 3-(3-pyridyl)alanine; PDGF, platelet-derived growth factor; Phe(pCl), 4-chlorophenylalanine; SCLC, small cell lung carcinoma; TGF, transforming growth factor; VIP, vasoactive intestinal peptide; PLG, poly(DL-lactide-co-glycolide).

are good reasons for emphasizing peptide receptors. The knowledge of characteristics and distribution of receptors for LH-RH and somatostatin and growth factors such as EGF and IGF-I may be important for the identification of hormone-responsive neoplasms, selection of a rational therapy and also may be of prognostic value for certain tumors [1–4]. A high content of receptors may permit localization of some tumors and metastases using scanning techniques with suitable radioligands [3, 5]. Information about membrane receptor levels may make feasible the projection of any possible direct effects of the analogs on certain tumors. In addition, the presence of binding sites for peptides such as LH-RH, somatostatin and bombesin/GRP in certain cancers can possibly be utilized for targeting various chemotherapeutic agents linked to suitable analogs, which act as carriers for these cytotoxic radicals [6, 7]. The sections of this review which follow focus on specific neoplasms and/or on the development of new classes of antitumor peptides.

PROSTATE CANCER

The inhibition of pituitary and gonadal function that occurs after chronic administration of agonists of LH-RH made possible a new approach for the treatment of prostate cancer and other sex hormone-dependent tumors [8]. Various clinical trials documented that [D-Trp^6]-LH-RH, Buserelin, Leuprolide or Zoladex can be successfully used for palliative treatment of patients with advanced prostate carcinoma. Initially, superagonists of LH-RH were given daily by the subcutaneous (s.c.) or intranasal route [8]. Subsequently, we developed a long-acting delivery system for [D-Trp^6]-LH-RH in microcapsules of PLG designed to release a controlled dose of the peptide over a 30-day period [9]. Recently we carried out a histological and immunohistochemical study on the microcapsules and microparticles *in vivo* [10]. We concluded that the release of [D-Trp^6]-LH-RH and other peptides from the PLG microcapsules or microparticles is controlled mostly by the speed of the biodegradation of the polymer matrix and the diffusion of the peptides from the PLG is negligible [10].

Sustained delivery systems that can be injected once a month make the treatment of patients with prostate carcinoma and other neoplasms more convenient and efficacious [8, 11]. However, the duration of remission in patients with prostate cancer is limited, as hormonal manipulations do not prevent the ultimate growth of hormone-independent cells [12]. Combination of hormonal therapy with somatostatin analogs might forestall this phenomenon and prolong survival [13]. Somatostatin analogs could inhibit prostate cancers by reducing the release of GH and prolactin and interfering with the action, signal transmission or secretion of endogenous growth factors. Growth factors, especially EGF and IGF-I, could be implicated in neoplastic proliferation of the prostatic cells. Our studies revealed the presence of membrane receptors for LH-RH, somatostatin and EGF in human prostate cancer specimens [4, 14]. We have also demonstrated that modern superactive octapeptide analogs of somatostatin, such as RC-121 and RC-160 significantly inhibit the growth of Dunning R3327 prostate cancers and, when given in combination with [D-Trp^6]-LH-RH microcapsules, potentiate the effects of the latter [15]. The combination of LH-RH agonists or antagonists with somatostatin analogs could result in an increase in the therapeutic response in patients with advanced prostate cancer [13]. Somatostatin analogs could be also tried in patients with prostate cancer who have relapsed to androgen ablation therapy [13].

LH-RH ANTAGONISTS

LH-RH antagonists represent another class of compounds that may be useful for treatment of hormone-dependent cancers. While repeated chronic administration of LH-RH agonists is required to inhibit LH and FSH release and reduce the levels of sex steroids, similar effects can be obtained with a single administration of LH-RH antagonists [8]. These antagonists act on the same receptor sites as LH-RH and cause an immediate inhibition of the release of gonadotropins and sex steroids. Since 1972, hundreds of LH-RH antagonists have been synthesized and tested.

Recently, new LH-RH antagonists free of edematogenic and anaphylactoid reactions were synthesized in our laboratory and tested *in vitro* and *in vivo* [16, 17]. These antagonists included [Ac-D-Nal(2)^1, D-Phe(4Cl)^2, D-Trp^3, D-Hci^6, D-Ala^{10}]-LH-RH (SB-29), [Ac-D-Nal(2)^1, D-Phe(4Cl)^2, D-Trp^3, D-Cit^6, D-Ala^{10}]-LH-RH (SB-30) and [Ac-D-Nal(2)^1, D-Phe(4Cl)^2, D-Pal(3)^3, D-Cit^6, D-Ala^{10}]-LH-RH (SB-75). These

new antagonists inhibited LH and FSH release in hypergonadotropic women for more than 20 h when given in doses of 300–600 μg (total), and caused no side effects [18]. Normal men showed an 80% fall in total and free serum testosterone levels 12 h after s.c. administration of 300 μg SB-75 [18]. Preliminary results in patients with advanced prostate carcinoma (D_2) treated with 300–500 μg SB-75 bid indicate persistent inhibition of serum LH and FSH levels and a fall in serum testosterone levels [18]. Recently, we obtained a marked inhibition of growth of Dunning R3327 prostate cancer in rats after treatment with microcapsules of antagonist SB-75.

In vitro studies indicate that agonist [D-Trp^6]-LH-RH, antagonists SB-29, SB-30, SB-75 and somatostatin analog RC-160 exert direct inhibitory effects on the growth of PC-3 and LNCaP human prostate cancer lines. Direct action of these analogs on tumors would increase their oncological application. The advantage of the antagonists would be that they inhibit LH, FSH and sex steroid secretions from the start of the administration. The use of antagonistic analogs of LH-RH for the treatment of cancer would avoid the transient stimulation of release of the sex steroid which occurs initially in response to LH-RH agonists, thus preventing the temporary clinical "flare-up" of the disease.

BREAST CANCER

About one-third of all breast cancers are estrogen-dependent. In addition, prolactin, growth hormone and various growth factors such as IGF-I, EGF and α-TGF may also be involved in growth and malignant transformation of human breast cancer cells [13, 19]. Human breast tumors and cancer cell lines such as MCF-7 have receptors for IGF-I and EGF [1, 2, 13, 19]. The presence of EGF receptors is associated with poor prognosis and advanced disease in patients with breast cancer. Somatostatin analogs might inhibit breast cancers by reducing the release of GH and prolactin and interfering with the action or secretion of endogenous growth factors.

In clinical trials carried out so far, regression of tumor mass and disappearance of metastases in premenopausal and postmenopausal women with breast cancer treated with [D-Trp^6]-LH-RH, Buserelin, Zoladex or Leuprolide have been described [8, 20]. Some direct antitumor effects of LH-RH analogs and somatostatin analogs on mammary carcinomas are also possible, since several groups found receptors for LH-RH and somatostatin in human breast cancer [1, 2, 4, 8, 13]. It should be possible to correlate the levels of these peptide receptors with clinical parameters to better identify endocrine-responsive neoplasms. This approach might be useful to guide a rational hormonal therapy in women with breast cancer [2].

In mice bearing MXT breast cancers, microcapsules releasing somatostatin analog RC-160 significantly inhibited the growth of the mammary tumors [21]. When changes in tumor volume in the treated groups were compared to the corresponding changes in controls, the combination of [D-Trp^6]-LH-RH and RC-160 was the most effective in inhibiting tumor growth. Histologically, the regressive changes in tumors caused by the treatment of RC-160, [D-Trp^6]-LH-RH and their combination were characterized by the coexistence of apoptosis (programmed cell death) and coagulation necrosis [21]. In the MXT model of mammary adenocarcinoma, LH-RH antagonist SB-75, administered in the form of microcapsules, resulted in 84% inhibition of tumor growth [22]. This inhibition was greater than that induced by ovariectomy. The regressive changes in the treated tumors were again characteristic of apoptosis. In view of its potency and an immediate inhibitory effect, LH-RH antagonist SB-75 might be considered as a possible new hormonal agent for the treatment of breast cancer [22]. The binding of antagonists SB-29, SB-30 and SB-75 to human breast cancers has been demonstrated. It has also been shown that in the MDA-MB-231 estrogen-independent human mammary tumor cell line in culture [23] LH-RH antagonists SB-29, SB-30 and SB-75 inhibited [^{3}H]thymidine incorporation into DNA as well as the rate of cell growth, measured by cell number [23]. These results support the concept that these new LH-RH antagonists can directly inhibit the growth of human mammary tumors.

One of the approaches for improving the therapeutic response in breast cancer could be based on a combination treatment using LH-RH agonists or antagonists with somatostatin analogs [13]. Somatostatin analogs are being tried as adjuncts to agonistic analogs of LH-RH in the palliative treatment of breast cancer in women, depending upon the status of receptors.

OVARIAN CANCER

Gonadotropins have been implicated in ovarian carcinogenesis [8, 24]. Suppression of the secretion of gonadotropins produced by LH-RH agonists inhibits the growth of ovarian epithelial cancers [8, 24]. LH-RH agonists may be useful for treating patients with advanced ovarian cancer who have relapsed after chemotherapy and those who cannot tolerate chemotherapy. Human ovarian epithelial cancers also have LH-RH binding sites [24]. Thus, some of the inhibitory effects of LH-RH agonists could be direct. Receptors for somatostatin and EGF have also been found in human ovarian cancers [4, 8]. Combination of somatostatin analogs such as RC-160 with LH-RH agonists or antagonists might improve the clinical response.

ENDOMETRIAL CARCINOMA

The involvement of estrogens in the pathogenesis of endometrial adenocarcinoma has long been recognized [8, 25]. A significant percentage of human endometrial carcinomas of different histological types shows high affinity receptors for LH-RH and EGF [25]. This could provide a rationale for the use of LH-RH agonists and antagonists for the management of endometrial carcinoma [25]. The principal mechanism by which LH-RH analogues could influence endometrial cancer may be estrogen deprivation, but in addition, a direct effect must be considered [25].

PANCREATIC CANCER

Various findings suggest that it might be possible to develop a hormonal therapy for exocrine cancer of the pancreas based on new somatostatin analogs in combination with LH-RH agonists and antagonists [8, 13]. Somatostatin analogs suppress the secretion and/or action of G.I. hormones (gastrin, secretin and cholecystokinin), which might influence the growth of the malignant cells of the pancreas [13]. Somatostatin analogs also inhibit the action or secretion of growth factors such as EGF and IGF-I, which are thought to be involved in neoplastic processes [8, 13, 26]. Sex steroids may also play a role in the growth of the cancerous pancreas [27]. The therapeutic effect of LH-RH agonists could be explained in part by the creation of a state of the sex steroid deprivation. A direct effect of LH-RH analogs on the tumor cells is also possible since our recent observations indicate the presence of [D-Trp^6]-LH-RH receptors in hamster pancreatic carcinomas and human pancreatic cancers [28]. Direct antiproliferative actions of somatostatin analogs could be also mediated by specific receptors located on pancreatic tumor cells [13]. High affinity binding sites for somatostatin and its octapeptide analogs RC-160 and RC-98-I have been found in normal human pancreatic tissues and in pancreatic tumors [4]. In contrast, Sandostatin (SMS 201-995) bound only to normal pancreas, not to human pancreatic cancers [4]. Antitumor properties of RC-160 and related analogs could be, in part, due to the fact that they bind to the receptors on the tumors [4] and in many cases inhibit the growth of these tumors. SMS-201-995 binds only to normal tissues [4], where it is antisecretory [26], but in pancreatic and other cancers does not induce tumor regression. Binding of RC-160 to the somatostatin receptor in the MIA PaCa-2 cell line activates dephosphorylation of EGF receptor [26]. Analog RC-160 causes the greatest stimulation of tyrosine phosphatase activity [26]. The Sandoz analog SMS 201-995 produces no significant tyrosine phosphatase stimulation or growth inhibition [26]. A marked inhibition of tumor growth occurs in hamsters with BOP-induced pancreatic cancer after treatment with microcapsules of somatostatin analog RC-160 or [D-Trp^6]-LH-RH [13, 29, 30]. The combination of both peptides produced the best results in terms of prolongation of survival, elimination of ascites and histological regression signs [13, 29, 30]. The increase of the dosage of RC-160 from 25 to 48 μg/day led to greater regression of tumors, and in combination with [D-Trp^6]-LH-RH produced an 85% reduction in tumor weight. Histologically, the tumors of hamsters treated with analogs showed striking regressive changes characteristic of apoptosis [30]. Chronic treatment with LH-RH antagonist SB-75 also causes a powerful inhibition of pancreatic tumor growth [31]. In cooperative trials, [D-Trp^6]LH-RH and RC-160 are being tried clinically as single drugs in patients with inoperable pancreatic cancer [8, 13].

COLORECTAL CANCER AND BRAIN TUMORS

Since sex steroids, G.I. hormones and growth factors may be involved in the tumorigenesis of the colon, an approach similar to that used on

pancreatic cancer and based on the combined use of analogs of somatostatin and LH-RH analogs could also be envisioned for colorectal cancer [13]. Bombesin antagonists could be also tried?

Recently, various brain tumors, including astrocytomas and meningiomas, have been found to contain significant levels of high affinity receptors for somatostatin [3–5]. The presence of receptors for EGF and IGF-I in human brain tumors was also established [13]. Iodinated ligands can be used for localization of tumors [3, 5]. It is possible that somatostatin analogs could inhibit the growth of some brain tumors. It was shown that analogs RC-160 and RC-121 penetrate through the murine blood–brain barrier [32].

SMALL CELL LUNG CARCINOMA

SCLC accounts for 20–25% of all cases of lung cancer. Most cases of SCLC are already metastatic at the time of diagnosis and although chemotherapy can be used, long-term survival is infrequent and new therapeutic modalities are needed [33]. Recent evidence indicates that SCLC may be hormone-dependent. SCLC produces peptides such as bombesin or GRP which act as autocrine growth factors. SCLC cell lines also have receptors for bombesin/GRP, and their clonal growth is stimulated by bombesin [33]. Consequently, the development of hormone therapy based on bombesin antagonists could be considered. The first competitive and specific receptor antagonist of bombesin/GRP was pseudotetradecapeptide [Leu^{13}, ψCH$_2$NHLeu^{14}]bombesin [34]. Subsequently, short-chain bombesin (6–14) nonapeptide analogs with a reduced peptide bond with higher potency were reported [35].

We have synthesized more than 30 [ψ13–14]bombesin (6–14) analogs with different modifications at positions 6, 7 and 14. These antagonists inhibit the binding of ^{125}I-labeled GRP(14–27) in a receptor binding assay on intact Swiss 3T3 cells. Some of these GRP/bombesin antagonists are active *in vivo*. Future studies will determine their possible application in a treatment of SCLC.

SYNTHESIS OF LH-RH ANALOGS CARRYING CYTOTOXIC RADICALS

Additional new classes of antitumor drugs are being developed by us based on LH-RH analogs containing various cytotoxic radicals such as melphalan and metal complexes related to cisplatin. LH-RH agonists and antagonists carrying various cytotoxic radicals were designed as targeted chemotherapeutic agents intended for treatment of cancers that contain receptors for LH-RH. Early compounds of this class have already been described elsewhere [6, 7].

Similar cytotoxic peptides containing chemotherapeutic agents are being designed for the treatment of cancers that contain receptors for somatostatin or bombesin/GRP. Such analogs could exert the effect of agonists or antagonists and, at the same time, act as chemotherapeutic agents targeted to the tumor cells by their peptide portions for which binding sites are present on the cell membranes. We may assume that a peptide containing a nitrogen mustard compound, such as Mel, or another radical can be bound to the membrane receptors and internalized. After endocytosis, such a compound could interfere with intracellular events in cancer cells. Recently, we made about 60 LH-RH analogs that contain various other cytotoxic radicals. The agonistic and antagonistic analogs containing cytotoxic radicals showed high biological activity *in vitro* and *in vivo*. Some agonists and antagonists containing cytotoxic radicals were found to bind with high affinity to the LH-RH receptors in human breast cancers and prostate cancers. In cytotoxicity tests in cultures of human breast cancer and prostate cancer cell lines, some analogs containing cytotoxic groups powerfully inhibited the [^{3}H]thymidine incorporation into DNA. Some of these compounds are being tested *in vivo*. Because the antitumor action may be exerted to a greater degree locally, or at least at more selective sites that have the cell membrane receptors, the peripheral toxicity would be reduced.

The availability of cytotoxic compounds linked to hormonal peptides that can be targeted to certain cancers possessing receptors for those peptides, and therefore more selective for killing cancer cells, could be of significant practical therapeutic importance.

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