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

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Many clinical approaches for the treatment of hormone sensitive tumors are being developed based on analogs of Luteinizing Hormone-Releasing Hormone (LH-RH) and somatostatin. Inhibition of 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 treatment of breast cancer and ovarian, endometrial and pancreatic carcinomas. Some of the effects of LH-RH analogs can be due to direct effects since LH-RH receptors have been found in these cancers. The use of sustained delivery systems based on microcapsules of Poly(D,L-Lactide-co-glycolide), which can be administered once a month, makes the treatment more practical and 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 which include the suppression of the secretion of the pituitary, pancreas, stomach and gut, interference with growth factors, and direct antiproliferative effects 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.

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CHOLECYSTOKININ AND GASTROINTESTINAL TUMOURS

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Cholecystokinin is a hormone secreted from the upper small intestine in response to feeding exerting powerful effects on gastrointestinal motility, endocrine and exocrine secretion, growth and possibly satiety. Our knowledge of the significance of this hormone has been greatly enhanced by the development of sensitive and specific radioimmunoassays for cholecystokinin and specific cholecystokinin receptor antagonists. The growth promoting action of cholecystokinin is mainly directed towards the pancreas. Longterm administration of cholecystokinin to rats induces pancreatic hypertrophy, hyperplasia and premalignant changes of the pancreas, while the hormone enhances the development of premalignant and malignant acinar cell tumours after administration of azaserine. Similar effects have been shown when endogenous plasma cholecystokinin levels were raised by dietary or surgical manipulation. These effects of cholecystokinin on pancreatic tumour growth could be inhibited by the administration of cholecystokinin receptor antagonists. The effects of cholecystokinin on pancreatic ductular cell carcinogenesis in the hamster after BOP administration are more controversal. Since it has been reported that some human pancreatic cancers have receptors for cholecystokinin and that the hormone stimulates growth of human pancreatic cancer in vitro or after transplantation into the nude mouse, blockade of the effects of cholecystokinin by receptor antagonists may be beneficial for human pancreatic cancer. However, until now it has not been shown that such receptor antagonists inhibit the growth of fully developed pancreatic cancer neither in the animal models nor in humans.

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SOMATOSTATIN RECEPTORS IN MALIGNANT TISSUES.

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High affinity somatostatin receptors (SS-R) have been identified in membrane homogenates or tissue sections from several hundred human tumors. SS-R were found in most tumors originating from SS target tissues, i.e. GH and TSH producing pituitary tumors, endocrine gastroenteropancreatic (GEP) tumors (including metastases), brain tumors including gliomas and neuroblastomas. SS-R were also expressed in several tumors originating from various other tissues, i.e. several breast and small cell lung carcinomas, some colorectal cancers and medullary thyroid carcinomas. In general, most of the SS-R positive tumors are well differentiated and/or have neuroendocrine features (pituitary, GEP, breast tumors, SCLC). They correlate with steroid-R status (breast tumors) and are negatively related to EGF-R status (pituitary, breast, lung tumors, gliomas, pancreatic Ca, but not meningiomas). In some tumors (i.e. breast tumors) SS-R are not homogeneously distributed, making SS-R autoradiography a particularly useful tool for assessing SS-R status. SS-R are functional in pituitary and GEP tumors, where they mediate hormone secretion inhibition. In these and in the other SS-R positive tumors, SS-R may also mediate antiproliferative effects, as evidenced in animals in which growth of SS-R positive tumor xenografts (SCLC, pancreatic or colon Ca) are inhibited by SS analogs. There is evidence that in breast tumors and neuroblastomas SS-R are favorable prognostic factors. For diagnosis, SS-R positive tumors and metastases can be localised in vivo by scanning techniques after 123I-SS analog injection.