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GOLD(III) INHIBITS ACTIVATED ADENYLATE CYCLASE IN HUMAN MG-63 OSTEOSARCOMA CELLS

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The influence of gold(III) (Au(III)) was studied on stimulatory and inhibitory regulations of the human MG-63 osteosarcoma adenylate cyclase. Treatment of intact osteosarcoma cells or membranes with Au(III) inhibited prostaglandin E_2-, isoproterenol-, and 5'-guanylimidodiphosphate (GppNHp)-stimulated adenylate cyclase activities with half-maximal inhibition occurring at 1 uM Au(III). In pretreated cells and pretreated membrane preparations basal cAMP levels, respectively, basal adenylate cyclase activities were not influenced by Au(III) up to 100 uM. Activation of the adenylate cyclase by Forskolin, its inhibition by low concentrations of GppNHp ($\leq$ 1 uM) were obliterated in Au(III) (10 uM)-pretreated membranes. Inhibition of activated adenylate cyclase by Au(III) occurred immediately after the start of the incubation. Au(III) inhibition of agonist-stimulated adenylate cyclase activity appeared to be independent of the concentration of Mg^{2+} added, indicating that Au(III) does not compete with Mg^{2+} for the binding site(s).
Our data indicate that Au(III) is a powerful inhibitor of the variously activated forms of osteosarcoma adenylate cyclase. Its non-differential effects suggest that Au(III) acts on the catalytic moiety of adenylate cyclase without affecting the activity of the component itself.

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CHARACTERIZATION OF AUTOSTIMULATORY AND TRANSFORMING GROWTH FACTORS FROM HUMAN BLADDER CARCINOMA CELLS

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The human bladder cancer cell line KK-47 releases into serum free culture medium an activity which stimulates its own growth. Production of such an autostimulatory activity is thought to be at least partially responsible for the growth of the tumor cells. The growth of the human bladder cancer cell line KK-47 ist associated with a alpha-TGF-production and a bladder growth stimulatory activity (BGSA). The transforming activity is characterized by stimulation of anchorage-independent growth of normal rat kidney fibroblasts and 125J-EGF-competition for bindin to A-431 cells. The BGSA stimulates the anchorage-dependent growth of bladder carcinoma cells in serum-free medium. When acetic acid extracts of KK-47 conditioned medium are subjected to Bio-Gel P-60 chromatography followed by C-18 HPLC, the majority of the alpha-TGFs elutes at 34 % acetonitrile, whereas the BGSA elutes at 38 % acetonitrile. The data indicate that growth of the KK-47 human bladder cancer cells is apparently partially dependent upon the autostimulatory activity BGSA, which is separable from the 125J-EGF competition activity produced by these cells.

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PEPTIDE HORMONES, SEROTONIN, AND OTHER CELL DIFFERENTIATION MARKERS IN BENIGN HYPERPLASIA AND IN CARCINOMA OF THE PROSTATE

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To explore the hormonal background for carcinoma of the prostate, a prospective and retrospective immunohistochemical investigation has been started, comprising not only carcinomas (n=40) but also benign nodular hyperplasia (n=80) and normal prostate glands (n=2). Applying the immunoperoxidase technique, using about 25 different antisera, raised against peptide hormones, serotonin (5-HT), neuron-specific enolase (NSE), and chromogranin A (ChrA), the occurrence of neuroendocrine cells in the parenchyma was analyzed, including a crude assessment of their incidence. Both in the normal and the hyperplastic prostate glands there were only four kinds of neuroendocrine cells, viz. 5-HT, TSH, somatostatin (Som), and calcitonin (CT) immunoreactive, argyrophil cells. Highly differentiated carcinomas displayed essentially the same pattern, but the anaplastic ones were found to contain great numbers of NSE & ChrA immunoreactive cells, showing not only 5-HT, TSH, Som, and CT immunoreactivity but also that against HCG-α, ACTH, enkephalin, β-endorphin, and glucagon.

An increased occurrence of neuroendocrine cells in poorly and moderately differentiated carcinomas of traditionally non-endocrine type was previously found in mucinous cystadenocarcinomas of the ovary. These observations may be used in the search for so-called tumour markers in clinical oncology.

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EFFECT OF PENTAGASTRIN ON CELL PROLIFERATION IN DMH-INDUCED ADENOCARCINOMA IN RATS.

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The trophic action of gastrin on the normal colonic mucosa is well documented while the influence of gastrin on colon cancer is still largerly controversed because histological methods and cell counts have never been used in these studies. Experimental colon cancer was produced in 24 male Wistar rats by weekly injections of 20 mg/kg of DMH during 24 weeks. The animals were then fasted for 24 hours and subdivided into two groups : 12 rats were given pentagastrin (120 µg/kg) by two separate injections within a 120 min interval; the control group received the excipiens (gelatin) alone. 16 hours after the subcutaneous injection 1 mCi.kg ^{3}HTdR was administered and the animals were killed. Autoradiographs from the tumors were prepared. Between 4000 and 16.000 cancer cells were counted in each tumor. The labelling index (LI) in the cancer cell population of the pentagastrin treated rats (21.49 $\pm$ 1.76%) was higher ($p < 0.01$) than the LI in the control group (14.76 $\pm$ 0.66%).
In a second experiment 20 DMH-treated animals were subdivided into two groups and received either pentagastrin by two separated injections or the excipiens alone. 20 hours after the administration of the peptide the rats of both groups were injected intraperitoneally with 1 µg/g body weight of vincristine sulfate (Oncovin - Lilly) and killed 4 hours later. In each tumor section the percentage of metaphases was determined. Cell counts ranged from 10.000 to 24.000 in each tumor section. The metaphase index (MI) in the pentagastrin treated group (49.08 $\pm$ 4,43%) was higher ($p < 0.01$) than the MI in the control group (23.54 $\pm$ 3.23%). These data show that acute administration of high doses of pentagastrin stimulates the proliferation of adenocarcinoma cells in vivo.