182

MODULATION OF DEVELOPMENT OF DIETARY FAT-PROMOTED (PRE)NEOPLASTIC PANCREATIC LESIONS IN BOP-TREATED HAMSTERS BY (ANTI)HORMONES

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In a previous study, surgical castration (SC) but not somatostatin (SMS) has been found to inhibit growth of preneoplastic acinar lesions in pancreas of azaserine-treated rats. In the present study, seven groups of 20 male hamsters were injected sc with 20 mg BOP/kg bw at 6, 7 and 8 wk of age. They were fed a high fat (20% corn oil) diet. Three groups were subjected to SC and treated sc (twice daily) with saline or aminoglutethimide (AGT; 2 mg/injection) or with SMS (osmotic pump; 3 µg/day). The other groups were treated with saline; AGT; SMS, or with Zoladex (depot formulation). At 4 months postinitiation the pancreata were examined for the number of dysplastic tubular ductal complexes, carcinomas-in-situ and (micro)carcinomas.

Results. (1) The number of dysplastic lesions was significantly ($p<0.05$) lower in the groups treated with SMS. (2) None of the other treatments siginificantly influenced the development of ductular pancreatic lesions.

Conclusion. It is recommended to use both animal models, the BOP-hamster and the azaserine-rat, in a comparative way for studying the effects of modulating factors on pancreatic carcinogenesis.

183

INHIBITION OF EXOCRINE PANCREATIC TUMOUR GROWTH BY SANDOSTATIN®

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Experimental and clinical trials suggest that it might be possible to develop a new hormonal therapy for pancreas cancer based on new somatostatin (SS) analogues.

SS14 is known to suppress the release of various hormones and peptides that induce exocrine pancreatic growth. The purpose of the current study was to determine whether a stable and long-acting SS analogue, Sandostatin® (SMS 201-995) could inhibit the growth of transplantable pancreatic tumours.

METHODS: Small fragments (~1 mm^3) of azaserine-induced pancreatic acinar carcinoma were inoculated s.c. in the scapular region of male Lewis rats. When tumours became palpable (10-15 days) the animals were divided into two groups receiving either SMS 201-995 (40 µg/kg/day) or saline delivered by means of osmotic mini-pumps for 14 days. Tumour volume was measured three times weekly and at the end of the experiment the tumours were excised, weighed and used for biochemical investigation and receptor autoradiography.

RESULTS: Treatment with SMS 201-995 decreased tumour volume by 80% ($p<0.001$) from the 2nd day and by 35-45% ($p<0.01$) at the end of the treatment period. Tumour weight and contents of protein, amylase, RNA and DNA decreased, respectively, by 52 ($p<0.05$), 46 ($p<0.05$), 76 ($p<0.01$), 63 ($p<0.01$) and 64% ($p<0.01$). Autoradiography with [^{125}I]-Tyr^3-SMS 201-995 on frozen tumour sections demonstrated the presence of specific SS receptors in high density in tumour tissue.

CONCLUSIONS: The present data indicate that SMS 201-995 (1) reduces the growth rate of the transplanted pancreatic tumour and (2) might exert its effect directly via specific SS receptors on the pancreatic tumour cells. The phenomenon of partial loss of activity during constant treatment is under further investigation.

184

CHARACTERISATION OF SOMATOSTATIN RECEPTOR (SR) EXPRESSION IN HUMAN COLO-RECTAL CANCER (CRC)

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Somatostatin is an inhibitory peptide involved in the regulation of cellular proliferation by receptor mediated activation of phospho-tyrosine phosphatase.
Aim: To identify and characterise SR expression in human CRC in terms of receptor affinity (equilibrium dissociation constant, Kd) and receptor density (maximum binding capacity, Bmax). We developed an assay for membrane bound SR utilising (I125) somatostatin-14 with rat cerebral cortex as positive control. The results were analysed by Scatchard analysis to provide the receptor affinity (Kd,nM) and receptor density (Bmax, pmol/mg protein). When applied to rat cerebral cortex a Kd of 0.9nM and Bmax of 0.24 pmol/mg protein was demonstrated (consistent with previous reports). This assay was applied to 20 consecutive CRC's and to adjacent "normal" mucosa. Of 20 tumours 18 expressed one class of SR with a Kd in the 100 nM range (median 200 nM) and a Bmax of 2.9 (0.6-10) pmol/mg protein. Similarly, 18 of 20 samples of colonic mucosa expressed SR with a similar Kd (median 180 nM) but a lower Bmax of 1.8(0.23-8.8) pmol/mg protein (NS). Thus SR expression occurs in the majority of human CRC. Studies on the effect of long acting somatostatin analogues at the receptor are indicated.

185

SOMATOSTATIN RECEPTOR (SR) EXPRESSION IN HUMAN GASTRIC ADENOCARCINOMA (GAC)

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Somatostatin is an inhibitory peptide with effects on cellular proliferation mediated by receptor induced activation of phosphoty-rosine phosphatase. We have developed an assay for cellular plasma membrane bound SR utilising (I125) somatostatin-14 with rat cerebral cortex as positive control. Scatchard analysis of data for rat cerebral cortex revealed a receptor affinity, Kd, of 0.9nM and receptor density, Bmax, of 0.24pmol/mg protein which are consistent with previous reports. The assay was applied to tumour and normal mucosal samples from 13 GAC patients taken from freshly resected specimens at operation. Of 13 tumours, 12 demonstrated specific binding for somatostatin One of these demonstrated a high affinity receptor (Kd=4.03nM, Bmax=0.229pmol/mg protein) and the remaining 11, intermediate affinity binding with a median (range) Kd of 80.9 (29.5-345) nM and median (range) Bmax of 0.765 (0.14-2.91) pmol/mg protein. There were no histologically distinguishing features of the tumour which expressed high affinity receptors. Conclusion: High affinity SR can accurately be demonstrated in GAC and intermediate affinity binding is almost universal. Further characterisation of this receptor and evaluation of the interaction of long acting somatostatin analogues at these sites is indicated.