OCTREOTIDE EFFECTS ON LIPID METABOLISM IN ACROMEGALY

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INTRODUCTION: Lipoprotein(a) [Lp(a)] is a strong independent risk factor for premature ischemic heart disease. Its levels are increased in acromegaly which is characterized by a high prevalence of cardiovascular complications. The somatostatin analog octreotide inhibits GH release and improves the course of acromegalic heart disease. Therefore, we studied short and long term octreotide treatment effects on lipid metabolism in acromegaly. PATIENTS AND METHODS: 14 acromegalic patients (pt) were studied. In every single patient the following parameters have been studied: glycaemia (BG)(mmol/L), HbA1c(%), total cholesterol (TC), C-LDL and C-HDL, triglycerides (TG)(mmol/L), ApoA1, ApoB(g/L), Lp(a)(mg/dl), GH and IGF-1(ng/ml). Those parameters were measured before (A) and after (P) one month of octreotide treatment in 12 pt and after 7 (1 pt) and 9 (1 pt) months of the same treatment in two other pt (0.1 mg x 3 s.c./die). RESULTS: Parameters (A) and (P) are summarized in the following table (all 14 patients)(Wilcoxon signed rank test):

	BG	TC	HDL	LDL	TG	Lp(a)	GH	IGF-1
(A)	5.9	5.52	1.27	3.91	1.59	47.7	41.4	895
(P)	6,5	5,32	1,24	3,79	1,62	29.4	28.1	865
p=	0.0236	ns	ns	ns	ns	0.0413	0.007	ns

Moreover, in diabetic acromegalics (2 pt) we observed higher Lp(a) values then in non-diabetic ones (12 pt) and the latters showed a greater octreotide-reduction in Lp(a) values (46 to 27 vs 56 to 41). CONCLUSIONS: Our data show that: 1) in acromegaly Lp(a) reduction is consensual to octreotide-induced GH reduction, 2) diabetes seems to exert a resistance on octreotide-induced Lp(a) reduction even if GH control seems to be prevalent.

SOMATOSTATIN ANALOG OCTREOTIDE (SMS 201-995) ENHANCES ENDOCRINE ANTICANCER TREATMENTS

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The therapeutic utility of tamoxifen and ovariectomy in the management of breast cancer is limited due to de novo resistance or relapse after a transient control of tumor growth. Thus, any strategy that would further enhance the efficacy of these widely used endocrine treatments would meet an important medical need. Therefore, we evaluated the effect of octreotide on the antineoplastic actions of tamoxifen. We used the DMBA-induced rat mammary tumor model which was shown to partially express somatostatin receptors and to be responsive to treatment with octreotide alone. In rats receiving octreotide and tamoxifen the total tumor burden/animal was significantly less than in rats treated with octreotide (minipump) or tamoxifen alone. At the end of the treatment period 3.7, 2.2, 1.6 and 0.2 tumors/rat appeared in animals treated with vehicle, octreotide, tamoxifen and the combination of octreotide and tamoxifen, respectively. The drug combination was well tolerated even at octreotide infusion rates of 50 µg/kg/h. Importantly, the tamoxifen-induced increase in uterine weight was significantly counteracted by co-administration of octreotide. We also investigated the antineoplastic effect of octreotide in combination with ovariectomy in the DMBA model. In overiectomized rats the marked regression of tumors induced by ovariectomy was frequently followed by tumor regrowth. However, continuous infusion of octreotide (50 µg/kg/h) suppressed this tumor regrowth. A single injection of a recently developed long acting release formulation of octreotide (Sandostatin-LAR®) in rats resulted in constant octreotide plasma levels over several weeks. The growth of DMBA mammary tumors was inhibited in a dose-dependent manner by this depot formulation. Further studies are warranted to investigate the modulatory role of Sandostatin-LAR® in endocrine treatment of breast cancer.

PHYTOTHERAPY WITH PERMIXON® MODULATES STEROID PATHWAYS IN BENIGN PROSTATIC HYPERPLASIA (BPH)

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The hexane extract of the fruit of the American dwarf palm, *Serenoa repens* (PERMIXON®), which is rich in unsaturated fatty acids, is now part of the armamentorium available to the urologist and general practitioner for the treatment of symptomatic benign prostatic hyperplasia (BPH).

This particular extract markedly influences the activities of several enzymes and receptors : (1) It inhibits 5-lipoxygenase and phospholipase A2 activity and, consequently, the formation of prostaglandins that mediate the inflammatory process. (2) It inhibits, by a non-competitive mechanism, the activity of both isoforms of the human 5α-reductase enzyme which converts testosterone into dihydrotestosterone (DHT) (K_i = 7.2 and 4.9 µg/ml for the Type 1 and Type 2 forms, respectively). We have expressed these isozymes in a baculovirus-directed insect cell system. (3) It inhibits the activity of 17β-hydroxysteroid dehydrogenase which metabolises 4-androstenedione into testosterone in primary cultures of epithelial cells and fibroblasts separated from BPH tissues (IC_{50s} = 40 and 200 µg/ml, respectively). (4) According to the literature, it can inhibit the activity of aromatase which converts androgens into estrogens. (5) It impairs the nuclear translocation of androgen and estrogen receptors.

On the other hand, Permixon® does not affect overall hormone equilibrium since it does not modify serum DHT and prostate-specific antigen levels in patients with BPH.

PERMIXON ® [LIPIDO-STEROLIC EXTRACT OF SERENOA REPENS (LSESr)] INHIBITS ESTROGEN/ANDROGEN-INDUCED PROSTATE ENLARGMENT IN THE RAT

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Inflammatory cell infiltration with an impairment of cell marker expression in the prostate may play a role in the development of BPH. In addition, previous studies have shown that the lateral prostate gland of Wistar rats is the site of a prostate enlargment that is age-related and hormone-responsive. Histologically, the prostate enlargment shows an accumulation of neutrophils in the lumina and mononuclear cells in the stroma. This inflammation process could be due to an imbalance between estrogen and androgen observed during ageing. In this paper, we propose to search for an *in vivo* inhibitory effect of LSESr in estrogen/androgen-induced prostate enlargment in the rat.

Wistar rats were castrated on day 1, implanted with a estradiol (E)-filled tubing on day 8, and with a testosterone (T)-filled tubing on day 22 to restore prostate weight. Prostate weight were evaluated in sham-implant rats and in (E+T)-implanted rats treated with or without LSESR (po, 50 mg/kg/day) after 30, 60 and 90 days of treatment. Histological examination was performed in some animals.

After 30 days of continuous hormonal combination, the weight of lateral (LP), dorsal (DP) and ventral (VP) prostate in (E+T)-implanted rats was increased in comparison with sham implant . After 60 days this effect is maintained but slightly decreased after 90 days. In LSESr-treated rats, after 30 days, a significant decrease of the weight of DP - 17,5% ($p<0,01$) and LP -10,5% ($p<0.05$) was observed. This decrease was further amplified after 60 days: -43,1% for LP ($p<0.01$), - 52,2% for DP ($p<0.01$); - 20,7 % for VP ($p = 0.02$). After 90 days, the decrease of DP and LP was still significant (-32.2%, and -45.5% respectively; $p<0.01$); in contrast, for VP, although the decrease was still evident (-13,7 %) it was not significant.

These results clearly demonstrate that LSESr is able to markedly inhibit the (E+T)-induced inflammatory process associated with prostate enlargment mainly localized in the lateral part in the rat. This effect is observed at a rat-adjusted human dosage and could explain the efficiency of LSESr in the managment of BPH.