Biomedicine & Pharmacotherapy
Volume 48, Supplement 1, 1994, Pages 25s-26s

Growth factors, cell proliferation and apoptosis in prostate adenoma

M. Colombel[a]

[a]Service d'urologie, hôpital Henri-Mondor, 51, avenue du Maréchal-de-Lattre-de-Tassigny, 94010 Créteil, France

Available online 19 February 2009.

Summary

Tissue growth, such as occurs in BPH, is the end result of an imbalance between the cellular proliferation rate and the cell death (apoptosis). In a previous study, we have already demonstrated an increased proliferative activity of basal cell areas of BPH, corresponding with an increased expression of EGF receptors on these cells. In this report, we examined and quantified proliferative (BrdU incorporation into nuclear DNA and Mibl immunostaining) as well as cell death (by *in situ* and labeling of fragmented nuclear DNA) markers to determine the extent to which the rate of these opposing processes are altered in BPH. In addition, we evaluated by immunostaining whether expression of the anti-apoptosis oncoprotein, bcl-2, is altered in BPH relative to normal prostate tissues.

http://www.ncbi.nlm.nih.gov/pubmed/11074529

Prostate. 2000 Nov 1;45(3):259-66.

Induction of apoptosis and inhibition of cell proliferation by the lipido-sterolic extract of Serenoa repens (LSESr, Permixon in benign prostatic hyperplasia.

Vacherot F, **Azzouz M**, **Gil-Diez-De-Medina S**, **Colombel M**, **De La Taille A**, **Lefrère Belda MA**, **Abbou CC**, **Raynaud JP**, **Chopin DK**.

Groupe d'Etude des Tumeurs Urologiques, Centre de Recherches Chirurgicales, Inserm EMI 99.09, Faculté de Médecine, Créteil, France.

BACKGROUND: To determine the mechanism by which prostate volume increases during the development of BPH and to evaluate the effect of LSESr (Permixon), a phytotherapeutic agent, we investigated apoptosis and cell proliferation in the stroma and epithelium of normal prostate and of BPH tissues from patients treated with or without LSESr.

METHODS: MIB-1 staining and the in situ end-labeling assay were used to evaluate the proliferative-apoptotic balance in normal prostates and in BPH tissues. Quantitative assessment was performed using an image analysis system.

RESULTS: In normal prostates, there was no significant difference between apoptotic and proliferative indices. Cell numbers and proliferative indices were higher in BPH than in normal prostates, while apoptosis values were similar. In the BPH treated group, LSESr significantly inhibited proliferation and induced cell death in both epithelium and stroma.

CONCLUSIONS: Induction of apoptosis and inhibition of cell proliferation are likely to be the basis for the clinical efficacy of LSESr.

Ph. Hug remark : see also :
http://en.wikipedia.org/wiki/Benign_prostatic_hyperplasia
and
http://wiki.medpedia.com/Saw_Palmetto
for rescue ! ! !

Mayday, mayday, mayday ! ! !

http://www.ncbi.nlm.nih.gov/pubmed/10458410

J Urol. 1999 Sep;162(3 Pt 1):927-30.

Differential RNA expression of the pS2 gene in the human benign and malignant prostatic tissue.

Colombel M, **Dante R**, **Bouvier R**, **Ribieras S**, **Pangaud C**, **Marechal JM**, **Lasne Y**.

Département d'Anatomo Pathologie, Hôpital Edouard HERRIOT, Lyon, France.

PURPOSE: The pS2 trefoil protein has been detected in close association with neuro-endocrine differentiation in prostate cancer and prostatic intraepithelial neoplasia. These preliminary results have suggested that pS2 is a candidate as a specific marker for prostate cancer tissue. To ascertain the specificity of pS2 in prostate cancer tissue, we have used an RT-PCR method from prostate biopsies provided from human malignant and benign prostatic hyperplasia (BPH) tissue.

MATERIALS AND METHODS: Prostate biopsies were obtained from transrectal biopsies from 153 patients with an abnormal DRE or a PSA more than 4 ng./ml. or symptoms of BPH and a PSA more than 4 ng./ml. Total RNA was extracted from fresh frozen specimens of tissue samples. Detection of pS2 transcript compared with GADPH transcripts was done using RT-PCR.

RESULTS: Biopsy results showed that 108 patients had prostate cancer (average Gleason score 6.39+/-0.74) and 45 patients had BPH. PS2 RT-PCR results showed that PS2 RNA expression was negative in 83% of the BPH cases. Conversely, 92% of prostate cancer specimens were positive (Chi-square: 86.09, $p<0.001$). There was no correlation with tumor stage or the Gleason score. Comparing the expression of pS2 in BPH and localized prostate cancer, we found a sensitivity of 92% and a specificity of 82%.

CONCLUSIONS: On this large sample of prostate biopsies from patients at risk of having prostate cancer, pS2 was demonstrated as an interesting marker significantly associated with prostate cancer. Further work on the expression of pS2 according to differentiation and hormonal status is in progress.

See also WiKi at :
http://en.wikipedia.org/wiki/Trefoil_factor_1
http://en.wikipedia.org/wiki/TFF2

Trefoil factor 1, also known as **TFF1**, is a human gene.[1]

Members of the trefoil family are characterized by having at least one copy of the trefoil motif, a 40-amino acid domain that contains three conserved disulfides. They are stable secretory proteins expressed in gastrointestinal mucosa. Their functions are not defined, but they may protect the mucosa from insults, stabilize the mucus layer, and affect healing of the epithelium. This gene, which is expressed in the gastric mucosa, has also been studied because of its expression in human tumors. This gene and two other related trefoil family member genes are found in a cluster on chromosome 21.[1]

Ph. Hug remark : With further studies reading ! ! ! Mayday, mayday, mayday !

http://www.ncbi.nlm.nih.gov/pubmed/10322394

Trends Endocrinol Metab. 1999 Mar;10(2):47-54.

Regulation of Apoptosis in the Prostate Gland by Androgenic Steroids.

Buttyan R, **Shabsigh A**, **Perlman H**, **Colombel M**.

College of Physicians and Surgeons of Columbia University, Department of Urology, Atchley Pavilion 11th Floor, 161 Fort Washington Blvd, New York, NY 10032, USA.

The prostate gland requires androgenic steroids for its appropriate embryological formation and postpubertal growth and, once at adult size, remains dependent on a continuous supply of androgens for its vitality and function. A reduction of the levels of circulating androgens will rapidly induce apoptosis of the cells of the prostate, leading to extensive glandular regression. Studies of rodent models of prostate response to castration have shown that there are some remarkable changes in the gene activity of prostate epithelial cells leading up to apoptosis. There is now evidence for a critical cell signaling pathway, regulated by c-fos expression, necessary for castration-induced apoptosis, as well as evidence that this signaling initiates an abrupt and transient alteration in the synthesis of fas antigen, p53, bax and bcl-2 proteins in the androgen receptor-expressing prostate epithelial cells, the cellular compartment that appears to be the most affected by castration. However, more recent studies suggest that these castration-induced effects on the prostate epithelial cells might be, at least in part, an indirect response to a critical reduction in blood flow to the prostate gland that precedes the onset of epithelial cell apoptosis. The castration effects on blood flow to the prostate gland seem to be related to vascular degeneration associated with apoptosis of a subset of prostate endothelial cells.

Ph. Hug remark : see also :
http://en.wikipedia.org/wiki/Androgen

http://www.ncbi.nlm.nih.gov/pubmed/15806208

Saudi Med J. 2005 Mar;26(3):405-10.

Comment in:
Saudi Med J. 2005 Sep;26(9):1487.

Biological and morphological effects on the reproductive organ of rats after exposure to electromagnetic field.

Ozguner M, **Koyu A**, **Cesur G**, **Ural M**, **Ozguner F**, **Gokcimen A**, **Delibas N**.

Department of Histology and Embryology, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey. mozguner@hotmail.com

OBJECTIVE: The biological effect of electromagnetic field (EMF) emitted from mobile phones is a current debate and still a controversial issue. Therefore, little is known on the possible adverse effects on reproduction as mobile phone bio-effects are only a very recent concern. The aim of this experimental study was to determine the biological and morphological effects of 900 MHz radiofrequency (RF) EMF on rat testes.

METHODS: The study was performed in the Physiology and Histology Research Laboratories of Süleyman Demirel University, Faculty of Medicine, Isparta, Turkey in May 2004. Twenty adult male Sprague-Dawley rats weighing 270-320 gm were randomized into 2 groups of 10 animals: Group I (control group) was not exposed to EMF and Group II (EMF group) was exposed to 30 minutes per day, 5 days a week for 4 weeks to 900 MHz EMF. Testes tissues were submitted for histologic and morphologic examination. Testicular biopsy score count and the percentage of interstitial tissue to the entire testicular tissue were registered. Serum testosterone, plasma luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels were assayed biochemically.

RESULTS: The weight of testes, testicular biopsy score count and the percentage of interstitial tissue to the entire testicular tissue were not significantly different in EMF group compared to the control group. However, the diameter of the seminiferous tubules and the mean height of the germinal epithelium were significantly decreased in EMF group ($p<0.05$). There was a significant decrease in serum total testosterone level in EMF group ($p<0.05$). Therefore, there was an insignificant decrease in plasma LH and FSH levels in EMF group compared to the control group ($p>0.05$).

CONCLUSION: The biological and morphological effects resulting from 900 MHz RF EMF exposure lends no support to suggestions of adverse effect on spermatogenesis, and on germinal epithelium. Therefore, testicular morphologic alterations may possibly be due to hormonal changes.

http://www.ncbi.nlm.nih.gov/pubmed/1589524

Physiologist. 1992 Feb;35(1 Suppl):S248-9.

The evaluation of biological efficiency of electromagnetic fields generated by implanted radiotelemetric transmitters used in space research on animals.

Klimovitsky VYa, **Loginov VA**, **Zagorskaya EA**, **Weissleder H**, **Drescher J**, **Hecht K**.

Institute of Biomedical Problems, Moscow, USSR.

The study was carried out in 50 male rats abdominally implanted with biotelemetric systems (BTS) or mock-up. The animals were provided with 12/12 light/dark schedule during 6-week experiment. The electromagnetic field (EMF) frequency was 455 kHz, magnetic induction near transducer was about 10(-2) mT. Circadian rhythm of the body temperature and locomotor activity was controlled in course of the experiment. The latter been finished, some tissues and the blood of the animals have been sampled to test corticosterone, testosterone, T3, T4 level in serum with radioimmunoassay and membrane permeability for Ca2+, Na+, K(+)-ATPase activity and charge changes in liver microsomes was detected. The probable ways of the EMF influence on whole body are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/10814886

Cancer Lett. 2000 Jul 3;155(1):105-14.

Inhibitory effects of low doses of melatonin on induction of preneoplastic liver lesions in a medium-term liver bioassay in F344 rats: relation to the influence of electromagnetic near field exposure.

Imaida K, **Hagiwara A**, **Yoshino H**, **Tamano S**, **Sano M**, **Futakuchi M**, **Ogawa K**, **Asamoto M**, **Shirai T**.

1st Department of Pathology, Nagoya City University Medical School, Nagoya, Japan. imaida@med.nagoya-cu.ac.jp

We have previously reported that exposures of F344 male rats to both 900 MHz and 1.5 GHz electro-magnetic near fields (EMFs) results in slightly decreased numbers and areas of glutathione S-transferase (GST-P)-positive liver foci, liver preneoplastic lesions in rats, in a medium-term liver bioassay (K. Imaida, M. Taki, T. Yamaguchi, T. Ito, S. Watanabe, K. Wake, A. Aimoto, Y. Kamimura, N. Ito, T. Shirai, Lack of promoting effects of the electromagnetic near-field used for cellular phones (929.2 MHz) on rat liver carcinogenesis in a medium-term liver bioassay, Carcinogenesis 19 (1998) 311-314; K. Imaida, M. Taki, S. Watanabe, Y. Kamimura, T. Ito, T. Yamaguchi, N. Ito, T. Shirai, The 1.5 GHz electromagnetic near-field used for cellular phones does not promote rat liver carcinogenesis in a medium-term liver bioassay, Jpn. J. Cancer Res. 89 (1998) 995-1002.). In both experiments, the melatonin serum levels were significantly decreased in both 900 MHz and 1.5 GHz exposed groups as compared with sham-exposed control group values. Therefore, changes of serum melatonin levels may modify the development of preneoplastic lesions in the livers of rats exposed by EMF. In order to clarify this question, the effects of different doses of melatonin (1, 5, 10 and 20 ppm in the drinking water) were analyzed in the same bioassay system employed for our previously reported EMF exposure studies. Six-week-old male F344 rats were given a single dose of diethylnitrosamine (DEN, 200 mg/kg b.w., i.p.). Starting 2 weeks later, they were treated with 0, 1, 5, 10 and 20 ppm melatonin in their drinking water for 6 weeks. Melatonin treatment were performed only during the night (between 18:00 to 09:00) in order to maintain their circadian rhythm, since serum melatonin levels are high at midnight. At week 3, all rats were subjected to a two-thirds partial hepatectomy. At week 8, the experiment was terminated and the animals were sacrificed. Serum hormone levels of melatonin, adrenocorticotropic hormone (ACTH), corticosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone at this time point were measured, only the first being elevated, **while LH and testosterone were reduced**. Although clear dose dependence was not apparent, both numbers and areas of GST-P-positive foci in the liver were decreased in the melatonin treated groups, this being significant for numbers in the 10 ppm melatonin group. Comparison of the current results with the previously reported findings for EMF exposure experiments, suggests that increase in melatonin serum levels is a possible reason for the associated tendency for decreased preneoplastic hepatocyte foci development.

http://www.ncbi.nlm.nih.gov/pubmed/19093523

Pak J Biol Sci. 2007 Dec 15;10(24):4519-22.

Effects of extremely low frequency electromagnetic fields on testes in guinea pig.

Farkhad SA, **Zare S**, **Hayatgeibi H**, **Qadiri A**.

Department of Biology, Faculty of Science, Urmia University, Iran.

This study is carried out to measure the changes in testosterone hormone level and changes in testes tissue on 36 adult male Guinea pigs that divided to 6 groups. Group A as control group exposed to nil Electromagnetic Field (EMF) for two hours per day for 5 days duration, group B exposed to 0.013 microT in 5 Hz to the Same duration period, group C exposed to 0.207 microT in 50 Hz in similar conditions, group D exposed for 4 h day(-1) for 5 days in 0.013 microT, group E tested in 0.207 microT as group D, group F used as controlled group exposed for four hours per day in nil electromagnetic field. Guinea pig blood was tested after 5 days. Then data analyzed by t-test. The results indicated a significantly difference between control group and tested group of four and two hours, testosterone level decreased ($p < 0.001$), also testes tissues were sampled and observed main tissue changes in some treatments.

Gynecol Oncol. 1998 Oct;71(1):64-71.

Selective potentiation of gynecologic cancer cell growth in vitro by electromagnetic fields.

Watson JM, **Parrish EA**, **Rinehart CA**.

Lineberger Comprehensive Cancer Center and Department of Pathology & Laboratory Medicine, University of North Carolina, Chapel Hill, North Carolina 27599-7295, USA.
jmwpooh@med.unc.edu

OBJECTIVE: Epidemiological data suggest that exposure to electromagnetic fields (EMF) may increase the risk of various cancers. We evaluated EMF effects on the in vitro growth response of human cell lines isolated from various reproductive tract tissues. We also assessed the effects of EMF on cisplatin- or paclitaxel-induced cytotoxicity.

METHODS: Endometrial, ovarian, and prostate cancer cell lines as well as immortalized endometrial stromal cells and immortalized ovarian epithelial cells were exposed continually to EMF. Proliferation was assessed by the metabolic activity assay, MTT, direct cell counting, and anchorage-independent colony formation in soft agar. Cytotoxicity induced by cisplatin or paclitaxel was assessed using the MTT assay.

RESULTS: Continuous exposure to EMF at field strengths of 2 G enhanced proliferation of two human prostate and three endometrial, but only one ovarian, cancer cell lines. EMF enhanced metabolic activity of cancer cells within 96 h and increased absolute cell number (anchorage-dependent proliferation) and colony-forming efficiency (anchorage-independent proliferation) over sham-treated controls. EMF had no effect on cytotoxicity induced by the chemotherapeutic agents Taxol or cisplatin.

CONCLUSIONS: Continuous exposure to EMF can enhance growth rates of transformed cells for some human epithelial cancers. Cancer cells from the steroid sex hormone regulated tissues of endometrium and prostate appeared to be more responsive to EMF than cells from ovarian cancers.

PMID: 9784321 [PubMed - indexed for MEDLINE]