Oncothermia Journal 1:41-42 (2010)

Effects far from equilibrium in electromagnetic heating of tissues

Dr. Oliver Szasz[2], Dr. Gabor Andocs[3], Prof. Dr. Andras Szasz[1,2,*]

(1) Department of Biotechnics, Faculty of Engineering, St. Istvan University,, Budapest, Hungary
(2) Oncotherm Group, Germany
(3) Department of Pharmacology and Toxicology, Faculty of Veterinary Science, St. Istvan University, Budapest, Hungary
**Corresponding author e-mail: Szasz.Andras@gek.szie.hu*

Effects far from equilibrium in electromagnetic heating of tissues

Dr. Oliver Szasz[2], Dr. Gabor Andocs[3], Prof. Dr. Andras Szasz[1,2]*
(1) Department of Biotechnics, Faculty of Engineering, St. Istvan University, Budapest, Hungary, (2) Oncotherm Group, Germany
(3) Department of Pharmacology and Toxicology, Faculty of Veterinary Science, St Istvan University, Budapest, Hungary,
*Corresponding author e-mail: Szasz.Andras@gek.szie.hu

Introduction: One of the very first treatment "technologies" for oncology is the regional heating of the tissues and body- parts, (hyperthermia, HT). This long history was not enough to be accepted as conventional treatment, facing mostly skeptic opinions among the oncology experts. The main reason is its controversial results and poor control, the missing of appropriate selective, controllable safe deep heat-delivery. Constrained balance of physiological feedback and the sophisticated transport network with very heterogenic tissue structures block applying the simple heating practices. This situation requests definite bioengineering tasks as well as new paradigm for the medical applications. The modern heating technologies based on electromagnetic interactions made a huge step ahead in this complex field, but not enough yet to solve some crucial problems in deep heating [1]. The commonly applied microwave and high radio-frequency (RF) radiation is challenged by the magnetic and capacitive heating techniques, applied lower frequencies. Oncothermia method, (OTM) heats by the dielectric loss in the various body electrolytes and makes possible to select between the tissues and concentrate on the malignant cells. Due to the constrained RF-current conduction of OTM, the complex impedance determines the actual flow-direction of the current. This could distinguish by the microscopic heterogeneity in the treated tissue [2].

Materials and methods: The relatively low frequency RF-current dominantly flows in the extracellular electrolyte. The energy absorption creates a temperature gradient through the cellular membrane, which drives non-equilibrium processes by constrained heat-flow through the membrane, [3]. The ion- and mass-flows could be well approached by Onsager's theory in the frame of non-equilibrium thermodynamic description. The polarization conditions are effectively approached in frame of β-dispersion of the aqueous electrolytes. The dose is measurable on the ignited chemical effects [4] instead of the temperature. The actual realization of OTM is capacitive coupled heating, using the constrained conduction of 13.56 MHz RF [5], amplitude modulated by time-fractal pattern [6], which is not limited by the thermal-energy [7]. In vitro and in vivo experiments were accomplished on identical 42 °C reference temperature by conventional HT and OTM methods, respectively. The experimental systems are in vitro cell-lines (HT29, B16, HepG2, A431) and their in vivo xenografts in nude mice. The changes of the adherent connections the cell membrane- associated effects (activation of the apoptotic signal transduction pathways, heat shock protein mediated stress- responses) were studied in vitro, while the cell-destruction mechanisms were investigated in vivo.

Results: Conductance differences between the cell-culture/tissue-parts automatically control the focus at cellular/tissue level. Due to the change of metabolic activity OTM acts selectively, which was proven in co-culture experiments. The emergent thermal- and electric-gradients force higher membrane permeability, larger intracellular pressure, imbalance of the ion-exchange, and finally challenges the membrane stability. An over-expression of HSP70 (heat-shock protein by 70 thousand Dalton weight) on the outer membrane was detected by immunohistology. Longer recovery after OTM was also measured. HSP production of OTM was compared to HT, measured by PCR and luciferase indicated gene measurements were also performed. Significant reconstruction of adherent connections of the cells could be detected in a time-delay after OTM, casued by the polarization conditions of the field gradients. This was not observed by HT. Experiments staining the double strains of DNA (DAPI) and enzymatic labeling of the strand-break of DNA (TUNEL- FICT) had shown the high rate of apoptotic cell deaths caused by OTM compared to the dominantly necrotic HT. This observation was supported with the follow-up the β-catenin development during 24h. Significant difference between HT and OTM was measured in vivo as well. Effective characteristic cell-destructions of tumor lesions was observed in such low temperature where HT was ineffective. Experiments by combination of the heating methods with various drugs (mitomycine, liposomal-doxorubicine, Tc-radiopharmacon labeled liposomes, etc.) also emphasize the definite advantages OTM versus HT.

Conclusions: The non-equilibrium thermodynamics makes OTM feasible to go over the difficulties of the problem of the selective deep-heating. With this new paradigm OTM could be a candidate in the branch of modern therapies in medical practice. OTM could be applied in various biomedical fields where the selection and the drug-targeting as well as the personalized treatment are important requests.

Acknowledgments: Authors acknowledge financial support of the Hungarian National Office for Research and Technology, application KMOP-1.1.4-07/1-2008-0083 and the Oncotherm Kft.

References:

[1] Szasz A (2006) Physical background and technical realization of hyperthermia, in: Locoregional Radiofrequency-Perfusional- and Wholebody- Hyperthermia in Cancer Treatment: New clinical aspects, (Eds: Baronzio GF, Hager ED), Springer Science Eurekah.com, Ch.3. pp. 27-59

[2] Szász A (2007) Hyperthermia a Modality in the Wings. Journal Cancer Research and Therapeutics, 3:56-66

[3] Szasz A, Vincze Gy, Szasz O, Szasz N (2003) An energy analysis of extracellular hyperthermia. Magneto- and electro-biology, 22:103-115

[4] Szasz A, Vincze Gy (2007) Dose concept of oncological hyperthermia: heat-equation considering the cell destruction. Journal of Cancer Research and Therapeutics, 2:171-181

[5] Szasz A, Szasz O, Szasz N (2001) Electrohyperthermia: a new paradigm in cancer therapy. Wissenschaft & Forschung, Deutsche Zeitschrift für Onkologie, 33:91-99

[6] Szendrő P, Vincze G, Szász A (2001) Pink-noise behaviour of biosystems. Eur.Biophysics J. 30:227-231

[7] Vincze Gy, Szász A, Szasz N (2005) On the thermal noise limit of cellular membranes. Bioelectromagnetics, 26:28-35