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Mitochondria of mice and men: Moderate magnetic fields in obesity and fatty liver

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ABSTRACT

This paper reviews insulin resistance associated with fatty liver which accompanies the metabolic syndrome or diabetes from obesity. Until recently, one hypothesis that has received little attention is that mitochondrial defects are the cause of metabolic syndromes or diabetes 2, fatty liver and insulin resistance. Another hypothesis is that moderate magnetic fields change gene expression. Ob/Ob mice when treated with 0.5 T direct current electromagnetic fields were found to increase their activity, lose weight and fat in a 6 day period. Gene array analysis of human embryonic stem cells in another experiment of 0.23–0.28 T static magnetic fields was conducted. Up-regulation of genes for insulin factors genes, peroxisome proliferative activity receptor were increased, and calcium channel gene and other genes for mitochondrial ribosomal protein S, and uncoupling protein 2. Down-regulation of tumor necrosis factor alpha and interleukin 6 were demonstrated for this transformation. Forkhead transcription factors are also up-regulated at 5 days. Accelerated liver detoxification by moderate magnetic therapy of obesogens that disrupt homeostasis of metabolism of lipids ultimately resulting in obesity is another hypothesis.

Background

"Obesity is epidemic in nearly every country in the world. The most likely explanation for the spread of this health problem is substantial lifestyle changes—from more reliance on automobiles and less on everyday physical activity, to the increasing availability of processed foods" according to Dr. William Dietz, from the Centers for Disease Control and Prevention [1]. Obesity is now considered one of the leading health problems with increased rates of certain cancers, heart disease, stroke and diabetes.

Until the last two decades, the prevailing solution for this problem was to restrict calories, make wise dietary choices and encourage exercise and behavior medication. The FDA has taken a number of appetite suppressants off the market starting with Fen/Phen and then recently Meridia due to side effects and failed recently to approve three others. In the genetic race to identify the molecular causation, over 100 genes for obesity have examined and about 50 proposed for fatty liver (NASH) or non alcoholic steatohepatitis, some of which are on both lists. In the 1990s there was much excitement about an animal model for obesity, Ob/Ob mice (Fig. 1) that lacked Leptin, a hormone which is important in the control of appetite. When given Leptin, the mice lost weight. However after much capital investment, time and effort, Leptin failed to perform the same feat in human obesity. This was labeled by the media as "the best laid plans of mice and men often go awry."

Medical hypothesis 1: the mitochondria are defective!

This paper will present two medical hypotheses to hopefully rectify this conundrum: The first hypothesis that has received little attention until recently is that mitochondria defects seen in the metabolic syndrome and diabetes mellitus 2 are one of the causes of this epidemic [2]. This may be one of the reasons it is so hard to lose weight with calorie restriction and exercise as we and our mitochondria, the powerhouse of the cell, age!

The mitochondria which are double-membrane organelles that strip electrons from fatty acids, sugars and amino-acids and accumulate them on the soluble electron carrier NADH and on proton – bound FADH2. NADH: ubiquinone reductase or (Complex I) is an enzyme that is located in the inner mitochondrial membrane that catalyzes the transfer of electrons from NADH to coenzyme Q (CoQ). It is the "entry enzyme" of oxidative phosphorylation in the mitochondria. FADH2 is flavin adenine dinucleotide (FAD) is a redox cofactor in metabolism which accepts 2 electrons and 2 protons. The electrons are passed down the mitochondrial respiratory chain to drive ATP synthesis by oxidative phosphorylation or coupled respiration. As the electron move down energy gradient from NADH/FADH to oxygen, redox energy is conserved by pumping protons across the inner membrane to build up an electrochemical gradient. Other essential metabolic functions include generation by the tricarboxylic acid cycle (Krebs) of numerous metabolites that function in cytosolic pathways, oxidative catabolism of aminoacids, ketogenesis, urea cycle and the generation of reactive oxygen species (ROS) which have important signaling functions. Additionally,

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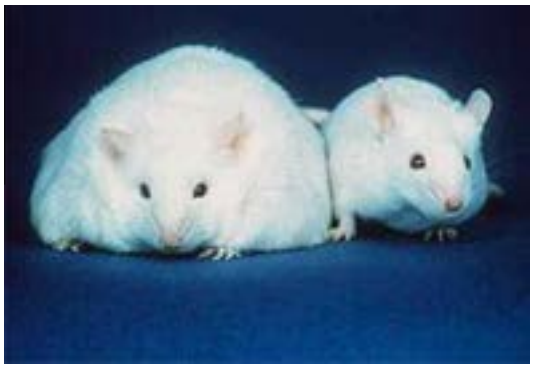

Fig. 1. A comparison of an Ob/Ob mouse unable to produce leptin thus resulting in obesity (left) and a normal mouse (right).

the mitochondrial control of calcium and protein cofactors is essential for cellular function and DNA repair [3].

Mitochondria use free energy from oxidative metabolism to generate a proton gradient across the inner membrane and channel this energy towards ATP synthesis to produce energy. Alternatively, the proton gradient may be dissipated or uncoupled by a specific mitochondrial protein termed UCP1 (Uncoupling Protein 1) at least in brown fat of rodents. UCP 2 is expressed in a variety of tissues including adipose tissue, heart, liver, muscle and pancreatic islets. UCP3 is 73% homologous to UCP2 in humans and predominately expressed in skeletal muscle and in rodent brown fat [4].

Mitochondrial function in the beta cells of the pancreas is highly regulated by the levels and activities of the UCP produced by the activity of the electron transport chain (ETC) in turn regulated by the reactive oxygen species (ROS). The levels and activity of UCP2 and the rate of ROS production are both increased by high fat diet, possibly through the direct actions of fatty acids. Patti and Corvera at the Joslin Diabetes Center hypothesized that the normal feedback loop is compromised by a direct activation of UCP2 by free fatty acids (FFA), as well as an effect of FFA to increase the amount of UCP2. They concluded that when uncoupling occurs to an excessive degree, compromising ATP synthesis enough to impair insulin secretion and (β) beta cell fitness [3].

Fig. 2 demonstrates the role of ß cell mitochondria in sensing increases in plasma glucose and inducing insulin secretion. Recently a hypothesis was proposed that suggests that overproduction of superoxide by the mitochondrial respiratory chain occurs during hyperglycemia. This occurs because hyperglycemia increases the flow of electrons to the respiratory chain by maintaining a large mitochondrial NADH/NAD to FADH2/FAD ratio. Therefore mitochondria in many tissues would spend more time under a state of low respiratory rate and reduced electron carrier, all favoring superoxide formation. In summary, increased mitochondrial ROS production during hyperglycemia may be a major factor in the pathology of diabetes [5].

As humans age, the brown fat reduces dramatically and is one of the theories of the metabolic theories of obesity. <http://www.en.wikipedia.org/wiki/Adipose_tissue>. Three recent articles in *New England Journal of Medicine* showed that adults have brown fat cells in their necks, where, as Sven Enerback of Goteborg University explains, has the unique ability to safely dissipate chemical energy in the form of heat [6]. When we spend a lot of time in the cold, the amount of brown fat we have goes up. In young men brown adipose tissue may be metabolically active and even though it reduced in overweight and obese subjects, it may make it a target for the treatment of obesity [7].

Another factor in obesity that recently has gained scientific impetus is the effect of obesogens on metabolism. By mimicking

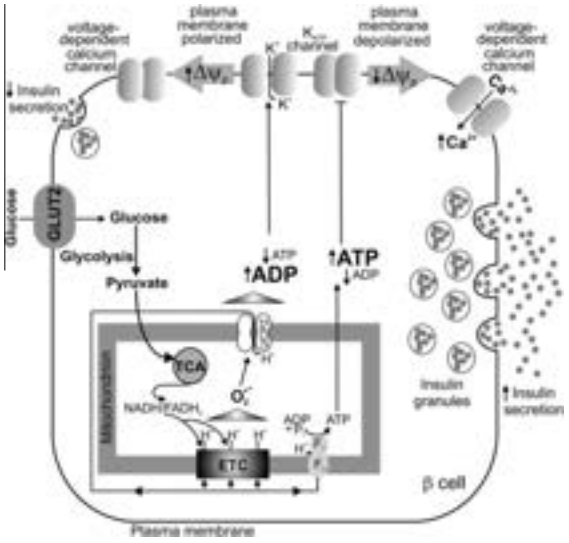

Fig. 2. Model of UCP 2 function in pancreatic β-cells. Elevated plasma glucose leads to increase in the cytoplasmic concentration due to uptake of glucose transporter (GLUT2). This increases the NADH/NASD ratio, elevated mitochondrial membrane potential and increase in ATP synthesis. The increase in ATP/ADP ratio causes closure of K ATP channels, leading to depolarization of the plasma membrane potential and influx of Ca, triggering insulin release. UCP2 activity dissipates the proton motive forces, lowering the ATP/ADP ratio and decreases insulin secretion. (Figure permission: Echtay K. Mitochondrial uncoupling proteins, what is their physiological role? Free Radic Biol Med Sci 2007;43:1351–1371.

the actions of naturally occurring hormones in the bodies of the obese patient, these endocrine disruptors can encourage the body to store fat and reprogram cells to become fat cells They also prompt the liver to become insulin resistant and prevent leptin from being released from fat cells to signal the body of satiety to reduce calorie intake. Diethylstilbestrol, bisphenol A, phthalates and organotins among others that target nuclear hormone receptor signaling pathways: sex steroid, retinoic X receptor peroxisome proliferative activity receptor – gamma (RXR–PPAR and glucocorticoid receptor (GR), have been identified and are termed obesogens. The ubiquitous presence of bisphenol A in the environment results from its use as the monomer in polycarbonate plastic and epoxy resins used to line food cans. In vitro studies have demonstrated the ability to synergize with insulin to promote proliferation and differentiation of preadiopcytes.

Plant derived phytoestrogens such as genistein and daidzein found in soy products have generally mimic estrogen action on adipogenesis and lipogenesis. Organotins used to increase the production of high value food crops, can inhibit aromatase, the key cytochrome P450 enzyme required for the conversion of androgens to estrogens. Additionally, estrogen receptor (ERRα) has been found to function in PPAR γ coactivation in mitochondrial biogenesis. Phthalates have been used as plasticizing agents to soften polyvinyl chloride products. These compounds act as agonist of the nuclear receptor PPARs α, -δ, that control lipid flux, adipocyte differentiation, and proliferation [8].

Medical hypothesis 2: moderate magnetic fields cause physiological changes

Moderate field (0.5 T) magnetic field DC therapy has been found recently to effective in an animal model of obesity and fatty liver which will be described in detail in the method section.

The fact that human and accordingly cellular life could respond to magnetic fields should not surprise anyone since from the beginning of life, cell forms, both plant and animal have coexisted

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in the milieu of the earth's magnetic field with adaptation and environment effecting the development of the species.

Molecules of cell membranes, over millions of years of evolution, have acquired the ability to sense, decipher, and to respond to low-level magnetic fields in the form of either periodic or randomly fluctuating signals [9].

The idea that static magnetic fields (SMF) can modulate signaling networks is based on reports that establish directional signals in development; repair and invasion are due to endogenous electrical fields [10]. Endogenous electrical fields from the body originate primarily from the brain and heart and EEG and ECG are commonplace diagnostic tests. In humans, MRI fields have been reported to affect the mood of severely depressed manic depressive patients [11]. Magnetic field stimulation at high magnetic flux densities is well known to influence many types of brain function with the mechanistic understanding that a strong oscillating magnetic field induces substantial electric current in the tissue [12]. At these high field magnetic stimulation used in transcranial magnetic stimulation (TMS) and in magnetic resonance imaging (MRI), magnetic flux densities are of the order of a few Tesla, some 10,000 times the natural occurring geomagnetic field. However with these field strengths, transcranial magnetic stimulation 1.5 T (Neurostar) has been approved by the FDA for the treatment of moderate depression. <http://www.en.wikipedia.org/wiki/Neuronetics>.

The molecular basis of how SMF can modulate signaling networks is based on reports that lipid bilayers acting as biosensors are capable of responding to magnetic exposure. Specifically, moderate strength SMF can change biophysical properties of membranes that include hyperpolarization [13], redox potential [14], and fluidity [15], thereby altering flux through sodium (Na^+) [16] and calcium (Ca^{2+}) channels [17]. As a result, changes in cytosolic concentrations of the calcium ion – which serves as a second messenger in several signaling pathways – occurs ubiquitously in cells exposed to SMF.

Wang and associates also hypothesize that in addition to altering the ion channel flux, biophysical changes to membranes may affect lipid raft microdomains that modulate downstream signaling. An example of this is the effect of ethanol on lipid rafts and the concomitant changes to toll like receptors 4 (TLR4) activity [18].

Tsong demonstrated that high field magnetic field strength was required to input sufficient energy to electrical couple mitochondrial membrane ATP and when using electrical pulses in short pulses to avoid Joule heating [19]. Observation meets the criteria of stochastic resonance where background noise coupled with weak signals in his experiment of human erythrocytes increased the amplitude or strength of that weak signal to about a 1000 times. Tsong has hypothesized that cells have their own languages for communication and that someday we will able to decipher this vibrational language to communicate with them, or even to control their activities and command their actions without chemicals [20].

Medical hypothesis of moderate DC electromagnetic field on obesity and fatty liver

Until the recently the mechanism of how moderate DC electromagnetic fields (DC EMF) affected animals and humans in health and disease was unknown.

The work of Wang, Kevin Yarema and his laboratory at Johns Hopkins has helped explain many of the beneficial effects seen in osteodegenerative and neurodegenerative disease states.

However, in the above paper there was no report of how the same DC EMF could affect obesity, insulin resistance, and fatty liver. This complex maze of multiple genes, impaired processes of metabolism, energy expenditure in human and mice in an environment of drugs, obesogens and excessive dietary calories along with aging make any one solution or therapy impossible. "Eat less and exercise more" has not relieved the obesity epidemic! The observations contained within this report, however when presented below, may well serve as an answer!

Analysis of gene data from the above study concerning the metabolic syndrome, diabetes and fatty liver not previously published was analyzed by this author and reported in this paper. The effect seen in Ob/Ob mice listed below as well as some human patients who were able to lose weight when all other previous attempts are therefore delineated in the remainder of this paper.

Method

Six almost 3-year old Ob/Ob knockout mice, which have no receptors for leptin and serve as an animal model for NASH (non alcoholic steatohepatitis) or fatty liver, were obtained from the Jackson Laboratory. These mice are obese and lethargic due to their metabolic derangement and usually die from their disorder shortly after their 3rd birthday. The mice were placed in a plastic cage with ad-lib access to mouse chow and water and then treated with 5000 gauss (0.5) T from poles of a DC electromagnet with a negative pole below and a positive pole of another electromagnet which were connected by a C arm of soft iron as seen in Fig. 3 [21].

This therapy was continued for seven consecutive days and has been discussed in detail by the author in another article [22].

Kevin Yarema, Wang and associates of the Whitaker Biomedical Institute of Johns Hopkins University used human embryoid body derived (hEBD) cells which were exposed to 0.23–0.28 T fields and mRNA microarray profiling to determine changes to global patterns of gene expression as outlined below and previously described.

Cell exposure to SMF was conducted for time intervals up to a maximum of 9 days using a device from the Advanced Magnetic Research Institute, International (AMRI Int., Calgary, AB) that fit into a standard TC incubator with sufficient clearance on all sides so that incubator functions (i.e., circulation of CO_2 and water saturated air) were not affected. The device was designed based on principles derived from clinical testing of SMF (Diabetic Peripheral Neuropathy (ClinicalTrials.gov Identifier: NCT00134524) and Chronic Low Back Pain (NCT00325377)) where the magnetic field was unidirectional with no reverse field passing through the sample. It was embedded with four 1″ × 4″ × 6″ in. permanent neodymium (NdFeB) rectangular block magnets with two located above and two below the central cavity (Appendix A: additional file 1).

Outcome

Ob/Ob Mice

The six male Ob/Ob mice began to increase their activity as soon as they were placed between the poles and moved as far away as

Fig. 3. DC EMF 0.5 T with patient between the 2 poles, above and below the table.

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possible from the 8 mm diameter of the magnets poles. Within 2 days they spent less time sleeping and more time eating. Within 4 days the mice were noticeable more active and actually started fighting each other for dominance and were visually leaner and after 5 days resembled normal mice. By 7 days when they were returned to the laboratory where the lead investigators mistook them as normal or wild strain brown mice. The mice were humanely sacrificed and their livers immediately frozen for later microscopic examination.

Known connections between Il-6 and other molecular players (e.g., Ca and TLR4) as well as ganglioside involvement in Il-6

Wang and associates performed mRNA profiling of SMF-treated cells coupled with analysis of the microarray data by the Ingenuity Pathway Analysis software tool verified that anticipated transcriptional changes – qualitatively consistent with the impact of altered Ca^{2+} flux or membrane domain fluidity on signaling pathways. They delineated known connections between IL-6 and other molecular players (e.g., Ca^{2+} and TLR4) as well previously unappreciated links (e.g., ganglioside involvement in IL-6 activation that acts even in the absence of SMF, offering a new controlling mechanism for IL-6. This study concluded by showing that SMF leads towards oligodendrocyte differentiation in human embryonic cells by preferentially stimulating pre-oligodendrocyte markers over the astrocyte markers usually associated with IL-6 exposure [18].

Cell cultures exposed to SMF, gene up and down regulation for metabolic syndrome, insulin resistance and NASH

As described previously by Wang and associates, the first tests of 15 min SMF exposure (followed by 1 day recovery) was based on reports that gene expression responded to magnetic exposure this quickly. After 1 day (~24 h) of SMF treatment, 379 genes were up-regulated and 549 were down-regulated with statistical significance even greater changes were seen after 4 or 5 days of exposure. However, the magnitude of change for most genes was modest. After 5 days of continuous SMF exposure, the number of genes up-regulated by >twofold increased to 85 while 94 were down-regulated to a similar extent. When the cells were allowed to recover for 1 day under normal culture conditions after 5 days of prolonged SMF exposure, the number of genes that remained up regulated by >twofold fell by almost half (from 85 to 47, whereas the number of down-regulated genes increase by 35.

Table 1 below list their findings of metabolic genes listed in this article expressed for 5 days with 1 day of recovery before analysis: (results not previously published) and inflammatory genes, some of which were previously published [18].

Discussion

Deficits in oxidative phosphorylation, glucose, and fatty acid disposal in various states of insulin resistance suggest that a common pathway of impairments in mitochondrial function contribute to the development of insulin resistance [23].

With the increasing population of insulin resistance in developed countries with its concomitant morbidities, the metabolic syndrome, diabetes, and obesity, the pharmacological solution to these problems is limited and the surgical solution with gastric bypass repugnant to many patients.

The increase in cirrhosis due to NASH has been projected to be the overwhelming cause for liver transplantation by the year 2015–2020 [24].

Insulin resistance

Insulin resistance plays a major role in the pathogenesis of the metabolic syndrome, fatty liver and type 2 diabetes. Magnetic resonance spectroscopy studies in humans suggest that a defect in insulin-stimulated glucose transport by inhibiting insulin-stimulated tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) and IRS-1 – associated phosphatidylinositol 3 kinase activity. A number of different metabolic abnormalities may increase fat delivery to muscle and liver as a consequence of either excess caloric energy intake or defects in adipocyte fat metabolism, and acquired or inherited defects in mitochondrial fatty acid oxidation [25].

Insulin like growth factor binding protein 3 (IGFBP3), insulin induced gene 2 (INSIG2), insulin receptor substrate (LEPR) and insulin receptor substrate 2 (IRS2) were all found to be up-regulated by SMF's above.

Ca^{++} transporting, plasma membrane 1 ATP2B1 was found to down-regulated to decrease the increased calcium influx seen in hyperinsulinemia [5].

Table 1
Gene expression for hEBD LVEC cells exposed to SMF for 5 days (i.e., Group 3) compared to control cells incubated without SMF exposure (Group 1).

Affymetrix probeset ID gene designation gene symbol ratio average signals (+ or −) fold-regulation control experimental
Up-regulated genes
207476_s_at interleukin 1 receptor-like 1 IL1RL1 (+) 3.465
212143_s_at insulin-like growth factor binding protein 3 IGFBP3 (+) 2.288
209566_at insulin induced gene 2 INSIG2 (+) 2.193
209894_at leptin receptor LEPR (+) 1.599
208998_at uncoupling protein 2 (mitochondrial, proton carrier) UCP2 (+) 1.538
209184_s_at insulin receptor substrate 2 IRS2 (+) 1.437
204131_s_at forkhead box O3A FOXO (+) 1.421
204132_s_at forkhead box O1A FOXO (+) 1.656
226978_at peroxisome proliferative activated receptor, alpha PPARA (+) 1.411
213714_at calcium channel, voltage-dependent, beta 2 subunit CACNB2 (+) 1.379
210008_s-at mitochondrial ribosomal protein S12 MRPS12 (+) 1.331
Down-regulated genes
210587_at inhibin, beta E INHBE (−) 4.12[a]
204475_at matrix metallopeptidase 1(interstitial collagenase) MMP1 (−) 3.98 [a]
207426_s_at tumor necrosis factor (ligand) superfamily, member 4 (tax-transcriptionally activated glycoprotein 1 TNFSF4 (−) 3.483
205207_at interleukin 6 (interferon, beta 2) IL-6 (−) 3.23 [a]
206026-s-at tumor necrosis factor, alpha-induced protein 6 TNFAIP6 (−) 2.277
21576_s-at ATPase, Ca ++transporting, plasma membrane 1 ATP2B1 (−) 1.456
206467_x-at tumor necrosis factor superfamily, member 6b, decoy TNFRSF6B (−) 1.381

[a] Data previously published [18].

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Chronic inflammation

Obesity is associated with chronic low-grade inflammation with an abnormal production of proinflammatory cytokines such as TNF-alpha in adipose tissue and muscle. Investigators in Milan found that TNF-alpha down-regulated e NOS with a concomitant reduction of mitochondrial biogenesis and function in white and brown adipose tissue and soleus muscle of 3 different animal models of obesity [26]. TNF alpha induced protein 6 (TNFAIP6) and TNF superfamily member 6b (TNFRSF6B) was found to down-regulated by SMF.

Adipose tissue IL-6 expression is increased in obesity and is a strong predictor of abnormalities in adipocyte and systemic metabolism. A study demonstrated that IL-6 impairs insulin signaling in both 3T3-L1 model of adipocyte model system and human adipocytes [27]. Interleukin 6 (interferon beta) IL-6 was also found to down-regulated by SMF.

Impaired oxidative phosphorylation

Impaired oxidative phosphorylation as a factor behind insulin resistance of skeletal muscle in type 2 diabetes was elucidated from results of Affymetrix gene profiling in subcutaneous and visceral fat of 8 patients. The investigators found the tissue and region-specific down-regulation of oxidative phosphorylation gene that is independent of obesity and at least in part mediated by TNF-alpha [28].

Mitochondrial oxidative capacity

Accordingly, it has been recently recognized that certain genes encoding for proteins that regulate mitochondrial biology are important in the development of insulin resistance. Researchers from the Karolinska Institute headed by Maria Kaaman have found a significant down-regulation in the expression of several electron transport chain genes selectively in type 2 diabetes mellitus in the visceral fat depot in obese patients. They suggested this decrease in cellular components to be mediated by TNF-alpha and found that the cytokines down-regulated the electron transport chain genes as well as significantly decreased the fatty acid oxidation in differentiated primary human adipocytes [29,30].

UCP's function to (a) export fatty acids anions from the mitochondria, (b) to regulate insulin secretion in the pancreatic β-cells and (c) to cause mild uncoupling and so diminish mitochondrial superoxide production. This protects against oxidative damage [31]. UCP2 was up-regulated by SMF exposure for 5 days.

Electron transport chain genes were up-regulated by SMF: calcium channel, voltage-dependent, beta 2 subunit CACNB2 and mitochondrial ribosomal protein S12 MRPS12.

NASH and mitochondrial abnormality

A study by Hideyuki Kojima and associates in a 2006 study demonstrated that in (NASH) nonalcoholic steatohepatitis, the enhanced oxidative stress is associated with hepatic inflammation and the degree of fat infiltration in the liver. However, when Zucker and their lean normal littermate rats were fed a choline-deficient diet and therefore, exposed to oxidative stress, both developed NASH. Zucker rats which naturally develop leptin receptor mutations, alone were associated with a mitochondrial abnormality. These findings indicate that a mitochondrial abnormality plays a role in the onset and progression of NASH in correlation with oxidative stress. Leptin-mediated neovascularization only occurred in the littermate rats, almost in parallel with fibrosis and cancer development as an expression of (VEGF) vascular endothelial growth factor [32].

A db/db mouse model of obesity, diabetes, and dyslipidemia has a deficient leptin receptor activity due to a homozygous point mutation in the gene for the leptin receptor. In db/db mice, induced swimming helped to overcome obesity by upregulating uncoupling proteins [33]. In Wang's study, Leptin receptor LEPR was upregulated by SMF.

FOXO3A, member of the family of Forkhead transcription factors also known as the longevity gene is up-regulated by SMF and in turn increases manganese-superoxide dismutase (MnSOD) and catalase, two of the major cellular antioxidant defense systems important for free radicals squelching [34].

Insulin signaling

The human Forkhead box O1A (FOXO1A) gene is also up-regulated according to Wang, Yarema and associates by SMF and is on chromosome 13q14.1 as a key transcription factor in insulin signaling in liver and adipose tissue. FOXO member's gene expression demonstrated temporal changes during starvation and refeeding [35]. It also plays a central role in the regulation of key pancreatic beta-cell genes by control of basal insulin receptor substrate 2 (IRS-2) [36]. Upregulation of IRS-2 in pancreatic cells prevents diabetes in obese and streptozotocin-treated mice [37].

In another animal model of fatty liver, using a liver specific IRS1and IRS2 double knockout (DKO) mice develop insulin resistance and hyperglycemia due to a substantial blockade of hepatic insulin signaling. FOXO1 is hyperactivated which dysregulates the expression of over 500 genes – including reduced expression of lipogenic genes. According to the authors, the DKO – liver accumulates triglycerides and free fatty acids impart to impaired mitochondrial oxidation. The number of mitochondrial is substantially reduced with additional defects in the electron transport chain which impairs NADH oxidation and NAD^+ regeneration needed for acyl-CoA dehydrogenase. A similar mitochondrial defect is seen in conventional insulin resistant ob/ob and db/db-mice [38].

Mitochondrial membrane and density

Obesity with high intake – associated lipid accumulation in muscle may interfere with cellular mitochondrial function through generation of reactive oxygen species leading to lipid membrane peroxidative injury and disruption of mitochondrial membrane-dependent enzyme. Exercise has positive effects on glucose metabolism, aerobic metabolism, mitochondrial density, and respiratory chain proteins in patients with metabolic syndrome. The authors proposed that these effects may be due to the exercise effect on (AMP) adenosine monophosphate kinase and a prospective physiological mechanism for this benefit was presented [39]. DC EMF may well increase mitochondrial density by up-regulation of mitochondria ribosomal protein (MRSPS12).

In our experiment, the mice when placed in the (DC EMF) direct current electomagnetic field were driven to lose weight by increasing their activity and metabolism dramatically. We hypothesize that the electromagnets by inducing a weak electric current in the bodies of the mice by Faraday induction, added electrons to the respiratory chain (ETC.) of their mitochondria enabling their dramatic change in their (ATP) adenosine triphosphate kinase and subsequent energy production. With more ATP production, the ATPase, Ca^+ transporting, plasma membrane 1 gene (ATP2B1) is down-regulated according to the data compiled by Wang at Johns Hopkins [18].

Adipose cell proliferation

Inhibin beta B (INHBB) expression has also been implicated in murine adipose tissue and regulated by leptin, insulin and dexamethasone [40].

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Its analogue Inhibin beta E has also been shown to be reduced by SMF.

PPAR – upregulation

PPAR-activation by various ligands, including derivatives of fatty acids and fibrates, stimulates the expression of several catabolic enzymes that are involved in mitochondrial and peroxisomal β-oxidation and microsomal ω-oxidation, as well as in the transcriptional regulation of genes that are necessary for the maintenance of the redox balance during the oxidative catabolism of fatty acids [41]. Additionally, a knock out mouse with the gene encoding the transcriptional coactivator peroxisome proliferator activated receptor gamma 1 alpha (PGC-1alpha) has been developed with mitochondrial abnormalities with increased body fat, hepatic steatosis and diminished mitochondrial number and respiratory capacity. The PGC-1 alpha mice were unable to maintain a core body temperature when exposed to cold and modest diminution in cardiac function [42]. Peroxisome proliferative activated receptor alpha (PPARA) was up-regulated by SMF.

Liver regeneration

Pulsed electromagnetic fields increased the rate of liver regeneration on rat liver after partial hepatectomy in an experiment by Ottani and associates. Using extremely low frequency EMF the massive accumulation of lipid droplets found in control rats following partial hepatectomy was also limited to one half of those animals exposed to EMF [43]. DC EMF has a similar effect on livers in Ob/Ob knockout mice with reduction of fat droplets. Its effect of liver regeneration has not been studied but is planned in the future.

Liver detoxification

Accelerated detoxification of the liver and fat of obesogens by DC EMF therapy is another hypothesis. Our clinical experience with over 10 years of patients treated with 0.5 T demonstrated the ability of magnetic acceleration of enzymatic acceleration and increased detoxifcation of chemical and possibly obesogens. Magnetic acceleration of enzyme reaction rate using milli-Tesla was demonstrated by Eichwald and Wallacezek [44].

In our limited human obesity experience, several patients when treated with DC EMF under an Institutional Review Board supervised study were then able to exercise, diet and lose weight dramatically beyond what they were able to do previously. One 40 year-old female patient who had never been able to lose weight went from a dress size of 20 to size 10 after 1 week of DC EMF therapy, and then 6 months of diet and exercise 6 days per week. One year later the same patient wore a size 2 for an impending wedding on the same diet and exercise regimen.

Summary

Obesity is a polygenic disorder with over 100 genes identified and fatty liver with at least 50 genes in NASH (fatty liver with inflammation) which leads to cirrhosis in 20–30% of patients. Attempts to ameliorate these disorders including diabetes or the metabolic syndrome with pharmaceuticals, has been disappointing and a number of the medication have been withdrawn from the market place. Only bariatric surgery such as gastric bypass or lap-band has demonstrated substantial metabolic outcomes but with added morbidity and mortality. Eat less and exercise more is only efficacious in very motivated younger patients. The reason is the mitochondrial defect with aging, inflammation, genetics and loss of estrogen. The results seen in Ob/Ob mice with DC EMF and the up-regulation of eleven metabolic genes demonstrated with SMF and down-regulation of 6 inflammatory and 1 calcium transport gene with SMF in two human embryonic stem cell lines provides support for this hypothesis. Direct current electro-magnetic fields are therefore hypothesized to be a potent polygenic tool in human obesity, metabolic syndrome and fatty liver.

Additionally, accelerated liver regeneration and accelerated obesogens detoxification from DC EMF are hypothesized!

Future prospects to defend these medical hypotheses and implement them

With proper funding for an in-depth examination of the mitochondria in Ob/Ob knockout mice after DC EMF therapy, and clinical trials in obese human patients from adequate venture capital: further elucidation of these phenomena will be possible. A new modality for upregulating metabolism and down regulating inflammation for weight reduction along with exercise, diet and behavioral therapy for obesity is desperately needed.

With over 10 years of clinical DC EMF therapy, very few side effects have been noted in over 3000 patients and with more experimental data on mechanisms and effects, regulatory approval should eventually follow after proper funding and focusing on a few clinical indications.

Conflicts of interest statement

None declared.

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Appendix A. Additional file

See Fig. A1 .

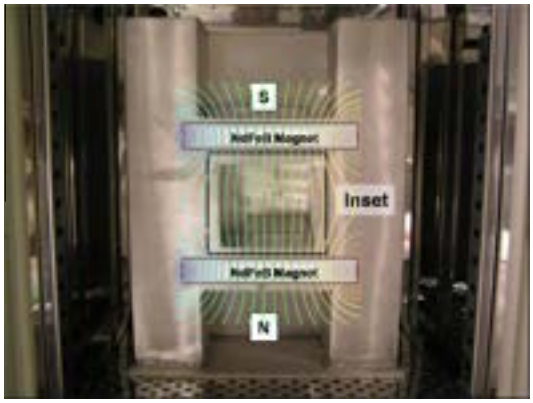

Fig. A1. Description of the SMF treatment device. The device used to treat cells with 0.23–0.28 T static magnetic fields is shown above along with field orientation and strength. <http://www.biomedcentral.com/content/supplementary/1471–2164-10–356-S2.ppt>.

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