print
ISSN 0250–6807

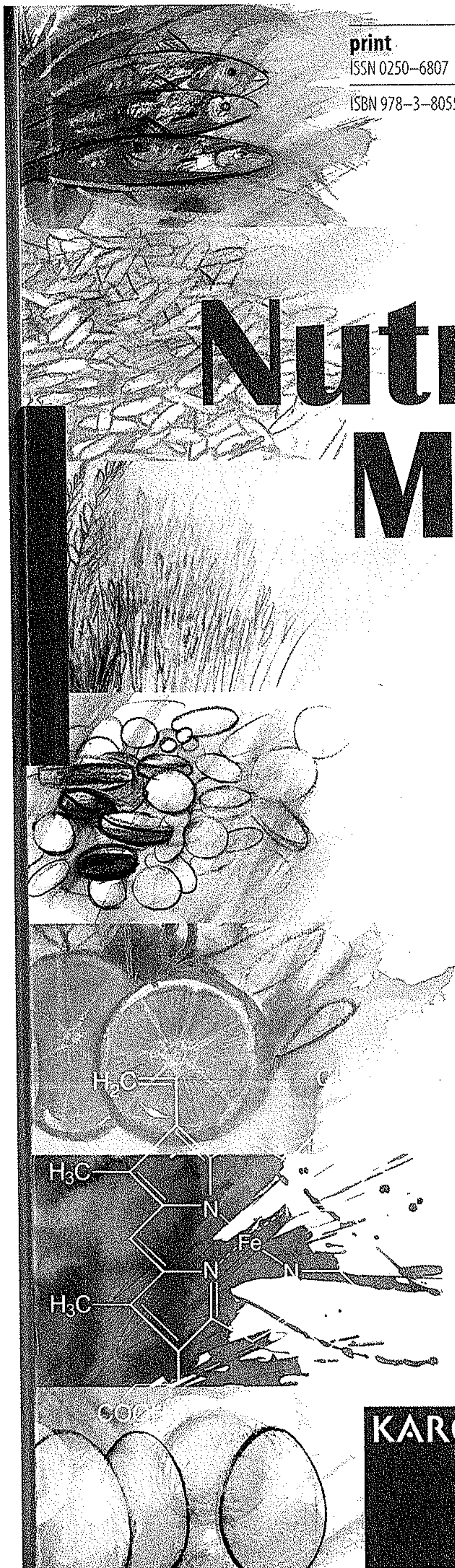
Ann Nutr Metab
51(suppl 1), 2007

51 | S1 | 07

online
ISSN 1421–9697

www.karger.com/anm

ISBN 978–3–8055–8335–0



Annals of Nutrition & Metabolism

An Official Journal of

International
Union of
Nutritional Sciences
(IUNS)

Federation of
European
Nutrition Societies
(FENS)

European Academy of
Nutritional Sciences

(EANS)

10th European Nutrition Conference

July 10–13, 2007, Paris, France

Abstracts

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algorithms. Another limitation in nutritional research is the relatively small effect of dietary interventions on physiological parameters. Similarly, the effects of nutrition on gene expression patterns are also hard to detect. Consequently, a suitable study approach is required along with the need to develop state-of-the-art sensitive micro-array analysis systems. Although a major technological advance, microarray technology has strengths and limitations that must be factored into the research design. A robust research hypothesis and study design will help to ensure the research question is adequately addressed by the experimental design (avoiding the so-called 'fishing experiments'). The use of adequate transgenic mouse models enhances significantly the success of the experiment and should be employed wherever possible. Once a transcriptomics study is performed, RNA quality and quantity should be verified and subsequent labelling and hybridization of RNA should preferably be conducted by the same technician and within the same microarray experiment. In order to enhance accuracy, pooling of samples is not desirable but increasing the number of biological replicates will decrease the false-positive rate and result in reliable data. Very important is the appropriate data preprocessing in particular with respect to the small changes in gene expression profiles requiring highly reliable algorithms. The most challenging part of the process occurs after the array data are obtained, when the data must be interpreted in terms of its biological meaning. Several commercial and non-commercial tools have been developed that assist with the extraction of significantly changed genes and the visualization of changed pathways or related networks.

As a paradigm for efficient use of microarrays in nutrition research we have used the analysis of genes that are regulated by peroxisome proliferator-activated receptors (PPARs). PPARs are ligand-activated transcription factors mediating the effect of unsaturated fatty acids and certain drugs on gene expression. Physiological they act as fatty acid sensors in metabolic active organs regulating a wide range of pathways allowing cells to modulate their function and metabolic capacity and flexibility. We have used state-of-the-art microarray analysis of organ samples from transgenes and intervention with highly specific PPAR-ligands that allows the characterization and comparison of organ-specific PPAR-related transcriptomes. Such 'organ transcriptome mapping' allows a comprehensive characterization of whole body biology that is under control of PPARs pointing to its physiological relevance. We have identified around 1,000–3,000 genes (depending on the organ) that are regulated in a PPARα-dependent way. This demonstrates the broad physiological impact of this fatty acid sensor and its relevance for nutrition.

Another important aim of our research is to study genome-wide influences of nutrition in particular of fats, with specific focus on the role of metabolic stress in the genesis of the metabolic syndrome, the collection of phenotypes combining inflammation, metabolic stress, insulin resistance, and diabetes. This goal is rather ambitious but based on the idea that nutrition should focus primarily on health and disease prevention and be complementary to pharmacological therapy, which targets the pathophysiological aspects of disease. To realize this goal, new genomics-based phenotypical biomarkers are needed that allow early detection of the onset of disease or, ideally, the pre-disease state of the metabolic syndrome, a condition we call metabolic stress. To approach this complex condition, molecular nutrition research on organ-specific dietary response patterns using transgenic and knock-out mouse models is combined with genomic technologies such as comprehensive microarray analysis. On a genomic level, these molecular changes serve as dietary 'signatures' or fingerprints that can precisely annotate the phenotype allowing comprehensive phenotyping, particularly under conditions of metabolic stress, early phases of organ-specific insulin resistance and decreased metabolic flexibility.

S19-1 Nutrition and the Ageing Process

Nutrition and ageing: Gene silencing or gene activation

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Genetic mechanisms may provide the best explanation of the ageing process. Five years ago, I had the pleasure of presenting my gene silencing theory of ageing. After determination of the sequence of the human genome, it was found that less than 2% of the genome codes for proteins and only 1/10 of these are active in adult life. This means that approximately 90% of our genes are silenced. The system of biological factors called epigenome consists of molecular switches that activate and silence the genes during our life (slide 1). This is an extremely complex system and it is expected to take another 25 years to fully understand it. Methylation of promoter sequences of the genes is the main mechanism for silencing both genes no longer necessary for development and the genes that are gradually turned off during the ageing process. Adult cells have an established methylation pattern in their DNA, but in the very first day of life, that methylation pattern is erased (slide 2). Most of the genes that are silenced later, are active during initial embryonal development, then they begin to be blocked through methylation and deacetylation, as their expression is no longer needed. A substantial group of genes are silenced after birth due to a transition from different living conditions in the uterus to the extra-uterine environment after birth. At the age of 25, the body has the optimal combination of active genes, but soon thereafter groups of genes are turned off as the result of ageing. Silencing of the genes is involved in hormonal changes during menopause, graying and loss of hairs, reduced immunity, detoxification and formation of cancer (slide 3). Down-regulation of tumor suppressor genes triggers increased activity of oncogenes, therefore increasing the risk of cancer. The continuous replacing of ageing cells is becoming less efficient and the body is accumulating damaged and malfunctioning cells due to less effective programmed cell death. The end result is that the promoters of silenced genes are covered with a coat of methyl groups and that 'good' genes are switched off and 'bad' genes are switched on. Genes work in a complex network in which silencing of some of them is increasing activity of competing genes. My theory of gene silencing in ageing was confirmed by studies of prominent groups of researchers in a number of different laboratories (slide 4). These studies performed in humans and animals confirmed that a substantial group of genes are silenced in ageing. At the same time, a small group of genes including oncogenes, chronic inflammation and those responsible for silencing of the other genes become overactive due to a disturbed balance between 'good and bad genes'.

The goal of age management therapy is to reverse age-related deterioration to the normal body function of a young adult (slide 5). On a molecular level, this translates to restoration of optimal gene expression; activation of silenced genes and normalization of overactive genes (slide 6). Our group isolated a number of small molecules existing in human blood, dairy products, and royal jelly which regulate expression of the genes and used them in cell cultures, animal studies and human clinical trials (slide 7). Among them are naturally-occurring and synthetically produced amino acid derivatives phenylacetylglutamine (PG), phenylacetylisoglutamine (isoPG), 3-phenylacetylamino-2,6-piperidionine (A10), phenylacetate (PN), and phenylbutyrate (PB). PG activates genes that are silenced in ageing including tumor suppressors *PTEN* and *MAD* and decreases expression of *AKT* oncogene (slide 8). PN works as a molecular switch that interrupts signaling in the *RAS* oncogene pathway and activates tumor suppressor *p53* and *p21* through decreasing methylation of the promoters. A10 is metabolized in the small intestine into PG and isoPG, and PB is metabolized in the liver into PG and PN.

The relationship between diet, lifestyle and longevity was known since antiquity. Ancient Egyptians knew the positive effects of proper nutrition on life extension (slide 9). While life expectancy of the general population was approximately 30 years, the ruling class lived much longer. Pharaoh Neferkare ruled for 94 years and Ramses II lived 92 years. One reason for the longer life expectancy of these rulers was a specially selected diet, which is documented in old scriptures and also confirmed by chemical analysis of archeological artifacts. It can be easily found from these data that almost 60% of 900 Egyptian remedies contained products of honeybees. Dietary ingredients and medicines coming from beehives were so important in ancient Egypt that bees had represented the kings of Egypt. The importance of these products was known to 5th century King Childeric of Franks. The glory of bees continued in France through the times of Napoleon who chose as his badge the heraldic golden bee. The bees make a perfect animal model to study of the relation between diet, ageing, and genetics (slide 10). Honeybee (*A. mellifera*) lives in three different social groups: workers, drones, and queens. The difference in longevity between these groups is tremendous. Workers live 5–6 weeks, drones – 10 months and the queens around 5–6 years (60 times longer than worker bees). The main factor that influences such great differences in longevity is diet – royal jelly. Workers larvae are fed with royal jelly for only 3 days, drones for 4 weeks, and the queen for her whole life. Since all of these three social groups carry the same genes, it is possible that the factors contained in royal jelly induce epigenetic changes in gene expression, which decide how long they live. By observing bees in my garden, I found that they have a preference for the flowers that are relatively unattractive to humans (slide 11). For instance, they favor tiny Mexican heather instead of the beautiful rose. Chemical analysis of flowers in our laboratory confirmed that Mexican heather contains high concentration of PG and PB compared to other flowers. The analysis of royal jelly revealed that it has approximately the same concentration of PG and PB (1.7%) as Mexican heather which may explain why this is a favorite flower for honeybees (slide 12). A series of experiments have been performed with PG and PB in the laboratory of Professor Paleolog in the Academy of Agriculture in Lublin. The preliminary results revealed approximately 5 times higher longevity in worker bees treated with PG and PB versus controls (slide 13). The dose response was documented for both PG and PB and the optimal dosage range in mg/kg was similar to that recommended for humans. The extracts of the organs were submitted for gene expression analysis. The preliminary results from bee longevity studies provide more attractive results than traditional experiments in fruit flies. In the best-known experiments conducted at Harvard University, it was possible to increase longevity 3 times by starving the insects and markedly reducing the quality of survival. Poor quality of survival is certainly not attractive, especially for western and southern European population. On the other hand, explanation of the mechanisms involved in 60 times longer survival in queen bees compared to workers may provide more attractive regimens for age management therapy.

The compounds studied by our team PG, isoPG, and A10 were formulated in a group of supplements and cosmetic products including Aminocare® A10, Aminocare® Extra, Aminocare® Brain Longevity Forte, Aminocare® Cream, and Aminocare® Lotion (slide 14). Oral administration of Aminocare® A10 resulted in prevention of cancer, increased energy, improved healing, cellular immunity, chronic joint inflammation and prostate hypertrophy; and also decreased wrinkles, blood cholesterol concentration, frequency of viral infection and benign breast nodules (slides 15–17). Aminocare® Brain Longevity Forte contains PG, curcumin, and piperine and is used to slow down the ageing of the brain, reduce inflammation, improve memory and prevent Alzheimer's Disease (slide 18). Aminocare® Cream and Lotion which contain PG, isoPG, and tamanu oil from French Polynesia provide excellent reduction of wrinkles and protection from skin cancer (slide 19). Clinical trials with Aminocare® Cream conducted at the University of Bordeaux confirmed statistically significant reduction of wrinkles.

In conclusion, ageing is associated with silencing of a substantial number of genes through the reaction of methylation of gene promoters and also increased activity of a smaller group of genes. A10, PG, isoPG, PN, and PB, which are dietary ingredients and are available in Aminocare® supplements and cosmetics, can restore optimal expression of certain genes (slide 20). Studies with these products indicated increased longevity in animal experiments in honeybees and an objective anti-ageing effect on the skin in human clinical trials.

S19-2 Nutrition and the Ageing Process

Mitochondria, ageing, oxidative stress and food restriction

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Abstract not received.

S19-3 Nutrition and the Ageing Process

Nutrition and the ageing immune system

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Ageing is a process in which oxidative stress, with excessive production of reactive oxygen species and decrease in antioxidant defences, occurs. This oxidative stress is a major contributing factor to the high morbidity and mortality that appears with age. Several studies have shown an age-related deterioration of the immune cell functions, with the leukocyte function being a good marker of health and longevity. We have observed that a subject showing premature