

Abstracts from Nippon Eiseigaku Zasshi (Japanese Journal of Hygiene) vol. 69, no. 2

© The Japanese Society for Hygiene 2014

Epigenetic Changes Caused by Intrauterine Malnutrition as Potential Disease Mediator and Early Prevention in Developmental Stages

Nippon Eiseigaku Zasshi, 69, 82–85 (2014)

Hideoki Fukuoka

Comprehensive Research Organization Waseda University

Presently, the incidences of noncommunicable diseases (NCD) have been increasing in both low- and middle-income countries worldwide. Effective long-term and multigeneration interventions to decrease the risk of NCD should be developed and introduced. The environment in utero alters phenotypes mainly through epigenetic mechanisms. The epigenetic changes induced in an unfavorable developmental environment have lifelong effects on cardiovascular and metabolic functions, susceptibility to cardiovascular disease, obesity, and other NCD. Although compared with animals, epigenetic analysis of human specimens is restricted except for peripheral blood, placental, or umbilical specimens, recently, important human studies have been reported concerning the epigenetic analysis of Line 1 gene from the umbilical blood, umbilical RXR α , or the peripheral nuclear cell IGF-2. The birth weight is an indirect marker of in-the-womb nutritional status. The incidence of low-birth-weight infants, weighing less than 2,500 g, has been increasing in Japan. Presently, it is higher than that in the latter half of the 20s Showa era, and is the highest among the OECD countries. This trend suggests that in Japan the intrauterine nutritional status has been deteriorating. We have to change this trend and put much attention on the pre-pregnancy and pregnancy nutrition for the present and future generations.

Effects of Exposure to Di(2-ethylhexyl)phthalate During Fetal Period on Next Generation—Possible Causes of the Plasticizer-Induced Offspring Toxicity

Nippon Eiseigaku Zasshi, 69, 86–91 (2014)

Yumi Hayashi¹, Yuki Ito², Tamie Nakajima³

¹*Pathophysiological Laboratory Sciences, Department of Radiological and Medical Laboratory Sciences, Nagoya University Graduate School of Medicine,* ²*Department of Occupational and Environmental Health, Nagoya City University Graduate School of Medical Sciences,* ³*College of Life and Health Sciences, Chubu University*

The concept of the Developmental Origins of Health and Disease (DOHaD) is bringing new insights into the origin of lifestyle diseases: unbalanced nutrition in utero and during infancy is associated with an increased risk of lifestyle diseases. In order to clarify this association, experimental and epidemiological studies have been conducted. Maternal exposure to di(2-ethylhexyl)phthalate (DEHP), an agonist of peroxisome proliferator-activated receptor α (PPAR α), decreases the number of live fetuses and newborn pups, and their body weights, and it enhances fetal desorption in wild-type mice. Similarly, these DEHP were also observed in mice expressing human PPAR α , but not in PPAR α -null mice. These results suggest that the DEHP toxicity in offspring is caused dependently on PPAR α . DEHP suppresses the increase in the levels of plasma triglyceride (TG)/fatty acids (FAs) only in wild-type pregnant mice, suggesting that the decreased lipid levels in utero may affect the fetus development, because TG/FAs are essential in the development of fetuses. Additionally, maternal DEHP exposure decreases estrogen and progesterone balances, which may also explain the effects on fetuses and pups mentioned above. Indeed, DEHP itself or metabolite(s) may induce the toxicity, because a difference in the metabolic route is observed between the wild-type and PPAR α -null mice. Thus, we were unable to conclude the causal factor(s) for the DEHP-induced offspring toxicity, that is, whether it is a direct or an indirect effect of the chemical or metabolite(s) via the toxic effects on maternal mice; however, PPAR α is indeed associated with in offspring toxicity.

Increase in Incidence of Hepatic Tumors Caused by Oncogenic Somatic Mutation in Mice Maternally Exposed to Inorganic Arsenic and the Multigenerational and Transgenerational Effects of Inorganic Arsenic

Nippon Eiseigaku Zasshi, 69, 92–96 (2014)

Keiko Nohara^{1,2}, Takehiro Suzuki¹, Shota Takumi³, Kazuyuki Okamura^{1,2}

¹Center for Environmental Health Sciences, National Institute for Environmental Studies, ²Graduate School of Life and Environmental Sciences, University of Tsukuba, ³Department of Public Health and Environmental Medicine, The Jikei University School of Medicine

Inorganic arsenic is a natural environmental contaminant and known to be a human carcinogen. Although rodent models are pivotal in elucidating the mode of action of arsenic, it has been difficult to verify the carcinogenicity of arsenic in rodents until recently. Waalkes et al. (Toxicol Appl Pharmacol 2003;186:7–17) reported that maternal exposure to arsenite increases the incidence of hepatic tumors in the male pups of C3H mice in adulthood. This finding indicated that the gestational period is vulnerable to arsenic. Using the same experimental model, we found that maternal arsenite exposure increases the incidence of hepatic tumors caused by a somatic mutation of the C61A Ha-ras gene, which encodes an activated oncogenic Ha-ras protein. The G:C to T:A transversion is attributable to oxidative stress. Our further studies of *gpt* delta transgenic mice, which enable detection of in vivo mutation, and genome-wide analysis of DNA methylation levels using the methylated DNA immunoprecipitation-CpG island microarray method suggest that oxidative-stress-induced mutation and DNA methylation changes are involved in the tumor augmentation in the pups maternally exposed to arsenic. Our recent study has also suggested that maternal arsenic exposure increases the incidence of hepatic tumors even in the grandchildren (the F2 generation). Consideration should be given to multigenerational and transgenerational effects of maternal exposure in future studies.

Physiological and Psychological Effects of Walking in Stay-in Forest Therapy

Nippon Eiseigaku Zasshi, 69, 98–103 (2014)

Bum-Jin Park¹, Yuko Tsunetsugu², Takeshi Morikawa², Takahide Kagawa², Juyoung Lee³, Harumi Ikei⁴, Chorong Song⁴, Yoshifumi Miyazaki⁴

¹Department of Environment and Forest Resources, Chungnam National University, ²Forestry and Forest Products Research Institute, ³Korea Forest Service, ⁴Center for Environment, Health and Field Sciences, Chiba University

Objective: To provide scientific evidence of the physiological and psychological effects of forest and urban environments on 47 young male adults undergoing stay-in forest therapy.

Methods: Field experiments were conducted at four sites in Japan. At each site, 12 subjects participated in the experiment. The experiments were conducted in forest and urban environments, and the subjects' physiological and psychological responses to these environments were compared. On the first day, six subjects were sent to a forest area, and the other six were sent to an urban area as controls. The groups were switched the next day. Heart rate variability and heart rate were measured to assess physiological responses. The semantic differential method for assessing emotions, the reports of "refreshed" feeling, and the Profile of Mood States (POMS) were used to assess psychological responses. The physiological and psychological responses of each subject were recorded during and after walking, and the differences in indices were compared between the two environments.

Results: The forest environment was associated with a higher parasympathetic nervous activity, a lower sympathetic nervous activity, and a lower heart rate than the urban environment. The subjective evaluation scores were generally in accordance with the physiological reactions and were significantly higher in the forest

environment than in the urban environment. POMS measurements showed that the forest environment was psychologically relaxing and enhanced psychological vigor.

Conclusions: This study provided clear scientific evidence of the physiological effects of forest therapy. The results will contribute to the development of forest therapy research and support the inclusion of forest therapy in preventive medicine.

Physiological and Psychological Effects of Viewing Forest Landscapes in a Seated Position in One-Day Forest Therapy Experimental Model

Nippon Eiseigaku Zasshi, 69, 104–110 (2014)

Harumi Ikei¹, Chorong Song¹, Takahide Kagawa², Yoshifumi Miyazaki¹

¹Center for Environment, Health and Field Sciences, Chiba University, ²Forestry and Forest Products Research Institute

Objectives: To clarify the physiological and psychological effects of a 1-day forest therapy.

Methods: The experiments were conducted at three sites, each containing a forest area and an urban area in Japan. Twelve male students participated at each of the three venues (total, 36 subjects). The subjects were randomly assigned to visit either the forest or urban area and were instructed to view the scenery in a seated position for 15 min. Heart rate variability and heart rate were measured to assess physiological response. The semantic differential method, reports of "refreshed" feeling, "state anxiety" in the State-Trait Anxiety Inventory (STAI) and Profile of Mood States (POMS) were used to determine psychological responses.

Results: Physiological data revealed that the subjects demonstrated significantly different responses to the forest and urban environments. For heart rate variability, the subjects showed a significantly higher ln(HF) and a lower ln(LF/HF) in the forest environment than in the urban environment. Heart rate decreased in the forest environment relative to that in the urban environment. The forest environment was perceived as significantly more "comfortable," "soothing," and "natural" than the urban environment after viewing. The score for "refreshed" feeling was also significantly higher. The score for the "state anxiety" in STAI was significantly reduced by viewing the scenery in the forested areas. The score for the "vigor" subscale of the POMS was significantly improved by viewing the scenery in the forested areas, whereas scores for negative feelings, such as "tension-anxiety" and "fatigue," were significantly reduced.

Conclusions: These results provided scientific evidence of the physiological and psychological effects of a one-day forest therapy.

Elucidation of the Physiological Adjustment Effect of Forest Therapy

Nippon Eiseigaku Zasshi, 69, 111–116 (2014)

Chorong Song, Harumi Ikei, Yoshifumi Miyazaki
Center for Environment, Health and Field Sciences, Chiba University

Objectives: The aim of this study was to elucidate the physiological adjustment effect of forest therapy based on the Law of Initial Value.

Methods: The experiments were conducted in nine forest and urban areas in Japan during the period from 2011 to 2012. There were 12 male Japanese university students participating in each of the nine

experiments (total, 108 participants). Of these, 98 subjects (mean age \pm standard deviation, 21.4 ± 1.6 years) were analyzed. The subjects were instructed to view a real forest landscape or urban area for 15 min. The systolic blood pressure, diastolic blood pressure, and pulse rate of each subject were measured. We analyzed the correlation between the initial values (after city viewing) and the differences in values between the two environments (after forest viewing–after city viewing).

Results: There was a negative correlation between the initial values and the differences in values between the two environments. The subjects whose initial systolic blood pressure, diastolic blood pressure, and pulse rate were high showed marked decreases in these parameters as their response after viewing the forest environment, whereas those whose initial systolic blood pressure, diastolic blood pressure, and pulse rate were low showed increases in these parameters as their response.

Conclusions: These results support the premise that the physiological effect of a forest environment can differ depending on a subject's initial response values. Moreover, it was clear that forest therapy caused physiological adjustment, normalizing blood pressure and pulse rate.

Possibility of Clinical Applications of Forest Medicine

Nippon Eiseigaku Zasshi, 69, 117–121 (2014)

Qing Li, Tomoyuki Kawada

Department of Hygiene and Public Health, Nippon Medical School

Since 2004, we have conducted a series of studies of the effect of forest therapy on human health and established forest therapy as a new preventive strategy. We have found that forest therapy has many beneficial effects on human health. However, there is almost no study dealing with the possibility of clinical applications of forest therapy. In this review, we discuss the possibility of clinical applications of forest therapy from the following viewpoints:

1. Forest therapy can decrease blood pressure, heart rate, sympathetic nerve activity, and levels of stress hormones, such as urinary adrenaline and noradrenaline, and can increase parasympathetic nerve activity, suggesting its preventive effect on hypertension.
2. Forest therapy can also decrease the scores for anxiety, depression, anger, fatigue, and confusion and increase the score for vigor in the Profile of Mood States (POMS) test, suggesting its preventive effect on mental depression.
3. Forest therapy can increase the activity and number of human natural killer (NK) cells and the intracellular levels of anticancer proteins, suggesting its preventive effect on cancers.
4. These findings suggest that forest therapy may have preventive effects on lifestyle-related diseases. However, the above preventive effects of forest therapy should be confirmed in clinical research.

Forest Medicine Research in Japan

Nippon Eiseigaku Zasshi, 69, 122–135 (2014)

Yoshifumi Miyazaki, Harumi Ikei, Chorong Song

Center for Environment, Health and Field Sciences, Chiba University

There has been growing attention on the effects of forest on physiological relaxation and immune recovery, particularly in forest

medicine research, from a perspective of preventive medicine. Japan is a world leader in the accumulation of scientific data on forest medicine research. In this review, we summarize the research that has been conducted in this area since 1992.

We conducted field experiment, involving 420 subjects at 35 different forests throughout Japan. After sitting in natural surroundings, these subjects showed decrease in the following physiological parameters compared with those in an urban control group: 12.4 % decrease in the cortisol level, 7.0 % decrease in sympathetic nervous activity, 1.4 % decrease in systolic blood pressure, and 5.8 % decrease in heart rate. This demonstrates that stressful states can be relieved by forest therapy. In addition, it should be noted that parasympathetic nervous activity was enhanced by 55.0 %, indicating a relaxed state. The results of walking experiments provided similar results. Li et al. demonstrated that immune function was enhanced by forest therapy in middle-aged employees who volunteered to participate in these experiments. Natural killer cell activity, an indicator of immune function, was enhanced by 56 % on the second day and returned to normal levels. A significant increase of 23 % was maintained for 1 month even after returning to urban life, clearly illustrating the preventive benefits of forest therapy.

In an indoor room experiment, we conducted tests with the following: (1) olfactory stimulation using wood smell, (2) tactile stimulation using wood, and (3) auditory stimulation using forest sounds. These indoor stimulations also decreased the blood pressure and pulse rate, and induced a physiological relaxation effect.

We anticipate that forest medicine will play an increasingly important role in preventive medicine in the future.

Molecular Mechanisms Underlying Copper Homeostasis in Mammalian Cells

Nippon Eiseigaku Zasshi, 69, 136–145 (2014)

Yasumitsu Ogra

Laboratory of Chemical Toxicology and Environmental Health, Showa Pharmaceutical University

Copper (Cu) is an essential metal for living organisms that utilize oxygen for respiration and is required as a cofactor of redox-regulating enzymes, such as superoxide dismutase, ceruloplasmin, lysyl oxidase, tyrosinase, and dopamine β -hydroxylase. However, the redox-active property of this metal may have toxic effects on cells due to the generation of harmful reactive oxygen species. Given these circumstances, it is said that cells have a dependable system for Cu homeostasis that efficiently distributes this essential metal to cuproenzymes, thereby preventing damage to proteins, nucleic acids, sugars, and lipids. In particular, influx, efflux, and intracellular distribution with maintenance of the oxidation state of Cu are strictly regulated. Several groups of Cu-regulating factors have been identified in mammalian cells, i.e., Cu transporters, Cu chaperones, Cu-binding proteins/peptides, and others. In this review, the features of the Cu-regulating factors are concisely examined in terms of molecular mechanisms underlying Cu homeostasis in cells.

Effect of Stone Spa Bathing and Hot-spring Bathing on Pulse Wave Velocity in Healthy, Late middle-Aged Females

Nippon Eiseigaku Zasshi, 69, 146–152 (2014)

Ikuharu Morioka, Yurina Izumi, Miyabi Inoue, Kanako Okada, Kaho Sakaguchi, Natsuki Miyai

School of Health and Nursing Science, Wakayama Medical University

Objectives: The purpose of this study was to clarify the effect of stone spa bathing (Ganban-yoku) and hot-spring bathing on brachial-ankle pulse wave velocity (baPWV) in healthy, late middle-aged females.

Methods: The subjects were 13 females (mean age 47.3 years). The skin and tympanic temperatures, blood pressure, and baPWV were measured before and after stone spa bathing and hot-spring bathing. For the stone spa bathing, the subjects lay down three times for approximately 10 min each time over warm stone beds.

Results: Although body weight showed no change after the hot-spring bathing, it significantly increased after the stone spa bathing. The increase was significantly related to the amount of water intake. The skin and tympanic temperatures increased to a smaller degree

after the stone spa bathing than after the hot-spring bathing. The diastolic blood pressure decreased to a smaller degree after the stone spa bathing. BaPWV showed no significant change after bathing both in the stone spa and in the hot-spring. The results of multiple regression analysis showed that the factors significantly related to the change in baPWV after the stone spa bathing were the changes in skin and tympanic temperatures and habit of smoking, and that after the hot-spring bathing was the change in skin temperature.

Conclusions: The results suggest that, compared with the hot-spring bathing, stone spa bathing causes less strain on the body. The stone spa bathing and hot-spring bathing showed no marked effect on baPWV. However, there is a possibility that the stone spa bathing may be used as a load for investigating arterial stiffness.