研究業績

論文等

免疫毒性学

Effective induction of oral anaphylaxis to ovalbumin in mice sensitized by feeding of the antigen with aid of oil emulsion and salicylate

Tomoko SHINDO, Yukiko KANAZAWA[1], Yoshiaki SAITO, Kohichi KOJIMA, Motoyasu OHSAWA, Reiko TESHIMA[2]

Journal of Toxicological Sciences, 2012; **37(2)**: 307-315

It is important to evaluate the ability of novel proteins in food crops and products to elicit potentially harmful immunologic responses, including allergic hypersensitivity. We developed a novel mouse model of food allergy involving an oral challenge of a protein antigen after feeding of the antigen in combination with modulating factors often ingested in daily life, namely, dietary oil emulsion and salicylate. In the model, BALB/c mice were sensitized orally for three weeks with ovalbumin (OVA) in linoleic acid/lecithin emulsion, followed immediately by intraperitoneal injection of sodium salicylate. At the end of the sensitization, the incidence of mice positive for serum OVA-specific IgG1 but not IgE had significantly increased in the combined-sensitization group. After the 3-week sensitization, a single or double oral challenge with OVA effectively and significantly caused severe anaphylaxis, as compared with the groups sensitized with OVA in the emulsion or the vehicle alone. Moderate increase of plasma histamine and intestinal abnormality in histology was found only in the combined-sensitization group. Anaphylaxis symptoms in the sensitized mice were induced more by oral challenge than by intravenous challenge, suggesting a critical role for the mucosal system. This is the first model for successful induction of oral anaphylaxis in mice sensitized by feeding of food protein without adjuvant. It will be useful to elucidate the mechanism of food allergy and to detect modulating factors of oral allergy at sensitization using this model, which simulates real life conditions.

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実験動物学

Male Hatano high-avoidance rats show high avoidance and high anxiety-like behaviors as compared with male low-avoidance rats

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Experimental Animals, 2012; **61(5)**: 517-524

Our prime objective was to establish an optimal model animal for studying avoidance learning and memory in rodents. The two-way rat inbred strains of Hatano high- (HAA) and low-avoidance (LAA) animals were originally selected and bred in accordance with their high or low performance respectively in the shuttle-box active avoidance task. Previous studies demonstrated that they have

clear strain differences in endocrine stress response, which is related to acquisition of aversive learning and emotional reactivity. To evaluate the effect of selection by the shuttle-box task on avoidance performance and emotional reactivity, male Hatano rats underwent passive avoidance, open field and elevated plus maze tests. The present results show that the avoidance performance in the passive task was significantly greater in HAA rats than in LAA rats. Furthermore, HAA rats showed high anxiety-like behaviors compared with LAA rats in open field and elevated plus maze tests. Taken together, this study demonstrated that 1) selection and breeding of Hatano HAA and LAA strain rats by shuttle-box task had been properly carried out with the criterion of high and low avoidance performance respectively and that 2) HAA rats were predisposed to high anxiety compared with LAA rats. These results indicated that Hatano HAA and LAA rats can be useful models for studying avoidance learning and memory.

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毒性病理学

PAM染色におけるコントロールサーベイ報告

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実験病理組織技術研究会誌, 2012; **21(1)**: 1-33

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第19回技術研修会グループミーティングのまとめ　実験病理技術全般について

島田美千代[1], 萩原　孝[2], 位坂清継[3], 五十嵐功[4], 国遠かおり[5], 前田圭子[6], 三好貴子[7], 山口　肇, 中野健二[8]

実験病理組織技術研究会誌, 2012; **21(1)**: 35-43

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第19回技術研修会アンケート集計結果報告　実験病理技術全般について

前田圭子[1], 五十嵐功[2], 位坂清継[3], 国遠かおり[4], 島田美千代[5], 萩原　孝[6], 三好貴子[7], 山口　肇, 中野健二[8]

実験病理組織技術研究会誌, 2012; **21(1)**: 45-52

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生殖・発生毒性学

Assessment of technical protocols for novel embryonic stem cell tests with molecular markers (Hand1- and Cmya1-ESTs): a preliminary cross-laboratory performance analysis

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Journal of Toxicological Sciences, 2012; **37(4)**: 845-851

The Hand1- and Cmya1-ESTs are novel short-term tests for embryotoxic chemicals using genetically engineering mouse ES cells for luciferase reporter gene assays. These ESTs allow convenient determination of differentiation toxicity and cell viability in a short duration with high throughput 96-well microplates for prediction of embryotoxicity of chemicals. To assess the Hand1-EST technical protocol, we firstly compared reporter gene assay and cytotoxicity test data for a representative compound (hydroxyurea) from four different laboratories with tests carried out under the same experimental conditions. Extensive investigations of the Hand1- and Cmya1-ESTs were then performed to explore reproducibility by comparing a set of 6 well-known test chemicals, including hydroxyurea, across the laboratories. The results gave good correspondence in all four laboratories, indicating that transferability, intra-laboratory variability and inter-laboratory variability of the present technical protocols of the ESTs were sufficient to conduct further validation studies.

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Ovariectomized mouse uterotrophic assay of 36 chemicals

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Journal of Toxicological Sciences, 2012; **37(5)**: 879-889

The concern over endocrine disruptors prompted international establishment of a strategic framework for the identification of the estrogenic compounds. OECD has launched the Conceptual Framework tool box containing various screening and testing methods including the uterotrophic assay. The (anti)estrogenicity of 36 chemicals suspected to be estrogen-receptor interactive by *in silico* and/or *in vitro* screening in the Extended Scheme for Endocrine Disruptor Screening and Testing of the Ministry of Health, Labour and Welfare, Japan, were monitored by the uterotrophic assay using C57BL/6J ovariectomized adult female mice after a 7-day exposure by oral gavage (po) and subcutaneous injection (sc). Ethynyl estradiol was used as reference for agonist and antagonist detection. In addition, Bisphenol A (sc) and Genistein (po) were tested for the comparison to rat assays. Among the 36, 2-[Bis(4-hydroxyphenyl)methyl]benzylalcohol, 2,2',4,4'-Tetrahydroxybenzophenone, 2,4-Dihydroxybenzophenone, 3,3',5-Triiodothyroacetic acid, New fuchsin and alpha-Naphtholbenzein, showed both estrogenic agonistic and antagonistic activities; first two showed U-shaped dose-response in antagonistic studies. N,N-Diphenyl-p-phenylenediamine, 2,2'-Dihydroxy-4,4'-dimethoxybenzophenone, n-Butyl 4-hydroxybenzoate, and Reserpine were agonistic by sc. Benzo [a] pyrene, Benz [a] anthracene, Dibenz [a,h] anthracene, 2-(2H-Benzotriazol-2-yl)-4,6-di(t-pentyl)phenol, Rosemarinic acid, meta-Thymol, 6-Gingerol, Colchicine, Malachite green base,

Fenbuconazole, and Lead acetate were antagonistic. The rest, i.e. n-Heptyl 4-hydroxybenzoate, Tetrazolium violet, Pravastatin sodium salt, Physostigmine, salicylate (1:1), Nordihydroguaiaretic acid, o-Cresolphthalein, 1,3-Dinitrobenzene, C.I. Pigment orange, Tetrabromobisphenol-A, 2-Hydroxy-4-methoxybenzophenone, Ethylparaben, Propyl p-hydroxybenzoate, Kaempferol, 2-(2-Benzotriazolyl)-p-cresol and Phenolphthalein were negative for both effects. Taking together with *in silico*/ *in vitro* screening, the result suggested that the ovariectomized mouse uterotrophic bioassay has sufficient performance comparable to rat for the screening of (anti)estrogenicity of various chemicals.

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Delayed reproductive dysfunction in female rats induced by early life exposure to low-dose diethylstilbestrol

Ryo OHTA, Hideo OHMUKAI, Hideki MARUMO, Tomoko SHINDO, Tomoko NAGATA, Hiroshi ONO

Reproductive Toxicology, 2012; **34(3)**: 323-330

A one-lifespan test was carried out to establish a test protocol for endocrine-disrupting chemicals (EDCs). Diethylstilbestrol (DES) was administered by oral gavage to neonatal rats at doses of 0.05, 0.5 and 5 μg/kg/day for 5 days after birth. Abnormal estrous cycles were observed throughout the study in all females from the 5 μg/kg group, and in 40% from the 0.5 μg/kg group from 24 weeks of age. The conception rate of 12-week-old females in the 5 μg/kg group was 0%, and that of the 23-week-old females in the 0.5 μg/kg group was 33.3%. No effect of DES was observed at the first parturition in any group, except for the 5 μg/kg group. However, litter size was significantly reduced in the 0.5 μg/kg group at the second parturition. These results indicated that a prolonged period of observation of reproductive function is necessary to determine EDCs reliably.

細胞毒性学

Prevalidation study of the BALB/c 3T3 cell transformation assay for assessment of carcinogenic potential of chemicals

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Mutation Research, 2012; **744(1)**: 20-29

The cell transformation assays (CTAs) have attracted attention within the field of alternative methods due to their potential to reduce the number of animal experiments in the field of carcinogenicity. The CTA using BALB/c 3T3 cells has proved to be able to respond to chemical carcinogens by inducing morphologically transformed foci. Although a considerable amount of data on the performance of the assay has been collected, a formal evaluation focusing particularly on reproducibility, and a standardised protocol were considered important. Therefore the European Centre for the Validation of Alternative Methods (ECVAM) decided to coordinate a prevalidation study of the BALB/c 3T3 CTA. Three different laboratories from Japan and Europe participated. In the study the following modules were assessed stepwise: test definition (Module 1) consisted of the standardisation of the protocol, the selection of the cell lineage, and the preparation of a

photo catalogue on the transformed foci. The within-laboratory reproducibility (Module 2) and the transferability (Module 3) were assessed using non-coded and coded 3-methylcholanthrene. Then, five coded chemicals were tested for the assessment of between-laboratory reproducibility (Module 4). All three laboratories obtained positive results with benzo[a]pyrene, phenanthrene and o-toluidine HCl. 2-Acetylaminofluorene was positive in two laboratories and equivocal in one laboratory. Anthracene was negative in all three laboratories. The chemicals except phenanthrene, which is classified by IARC (http://monographs.iarc.fr) as group 3 "not classifiable as to its carcinogenicity to human", were correctly predicted as carcinogens. Further studies on phenanthrene will clarify this discrepancy. Thus, although only a few chemicals were tested, it can be seen that the predictive capacity of the BALB/c 3T3 CTA is satisfactory.

On the basis of the outcome of this study, an improved protocol, incorporating some changes related to data interpretation, has been developed. It is recommended that this protocol be used in the future to provide more data that may confirm the robustness of this protocol and the performance of the assay itself. During the study it became clear that selecting the most appropriate concentrations for the transformation assay is crucial.

[1]Harlan Cytotest Cell Research GmbH; [2]European Centre for the Validation of Alternative Methods, Institute for Health and Consumer Protection, Joint Research Centre of the European Commission

Recommended protocol for the BALB/c 3T3 cell transformation assay

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Mutation Research, 2012; **744(1)**: 30-35

The present protocol has been developed for the BALB/c 3T3 cell transformation assay (CTA), following the prevalidation study coordinated by the European Centre for the Validation of Alternative Methods (ECVAM) and reported in this issue. Based upon the experience gained from this effort and as suggested by the Validation Management Team (VMT), some acceptance and assessment criteria have been refined compared to those used during the prevalidation study. The present protocol thus describes cell culture maintenance, the dose-range finding (DRF) experiment and the transformation assay, including cytotoxicity and morphological transformation evaluation. Use of this protocol and of the associated photo catalogue included in this issue is recommended for the future conduct of the BALB/c 3T3 CTA.

[1]Harlan Cytotest Cell Research GmbH; [2]European Centre for the Validation of Alternative Methods, Institute for Health and Consumer Protection, European Commission Joint Research Centre

Photo catalogue for the classification of foci in the BALB/c 3T3 cell transformation assay

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Mutation Research, 2012; **744(1)**: 42-53

This catalogue is a display of focus photos representative of the BALB/c 3T3 cell transformation assay (CTA). It is intended as a visual aid for the identification and the scoring of foci in the conduct

of the assay.

A proper training from experienced personnel together with the protocol reported in this issue and the present photo catalogue will support method transfer and consistency in the assay results.

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平成22年度「日本薬局方の試験法に関する研究」研究報告　輸液用ゴム栓試験法の見直し研究（第4報）
―ゴム栓試験法：細胞毒性試験における試料溶液の調製方法に関する検討―

柘植英哉[1], 大内　正[1], 森　充生[1], 下田耕三[1], 大庭澄明[1], 青木光夫[2], 林　美則[2], 五島隆志[2], 山影康次, 渡辺美香, 田中憲穂, 小島　肇[3], 四方田千佳子[3]

医薬品医療機器レギュラトリーサイエンス, 2012; **43(5)**: 473-482

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遺伝毒性学

Molecular mechanisms of apoptosis induction by 2-dodecylcyclobutanone, a radiolytic product of palmitic acid, in human lymphoma U937 cells

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Apoptosis, 2012; **17(6)**: 636-645

The irradiation of fat-containing food forms 2-dodecylcyclobutanone (2-DCB) from palmitic acid (PA). In this study, we investigated whether 2-DCB and PA induce apoptosis in human lymphoma U937 cells. We found that cell viability decreased by 2-DCB and apoptosis was induced by 2-DCB and PA. 2-DCB and PA significantly enhanced the formation of intracellular reactive oxygen species (ROS). Apoptosis induced by 2-DCB and PA was strongly prevented by an antioxidant, *N*-acetyl-*L*-cysteine. The treatment with 2-DCB and PA resulted in the loss of mitochondrial membrane potential, and Fas, caspase-8 and caspase-3 activation. Pretreatment with a pan-caspase inhibitor (z-VAD) significantly inhibited apoptosis induced by 2-DCB and PA. Moreover, 2-DCB and PA also induced Bax up-regulation, the reduction in Bcl-2 expression level, Bid cleavage and the release of cytochrome *c* from the mitochondria to the cytosol. In addition, an increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) was observed after the treatment with 2-DCB and PA. Our results indicated that intracellular ROS generation, the modulation of the Fas-mitochondrion-caspase-dependent pathway and the increase in $[Ca^{2+}]_i$ involved in apoptosis are induced by 2-DCB and PA in U937 cells.

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Tissue sample preparation for *in vivo* rodent alkaline comet assay

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Genes and Environment, 2012; **34(1)**: 50-54

The Japanese Environmental Mutagen Society/the Mammalian Mutagenicity Study group conducted a collaborative study to investigate whether cell nuclei or whole cells might be more suitably used to correctly detect genotoxic chemicals in the *in vivo* rodent alkaline Comet assay. Four participating laboratories applied four sample processing methods, i.e., three homogenization methods using the usual Potter-type shaft, a customized (loose) Potter-type shaft, or a Downs-loose-type shaft, for preparing cell nuclei, and the mesh membrane method for preparing whole cells, to the male rat liver. Homogenization with the usual Potter-type shaft clearly produced damage of the cell nuclei and DNA, while the other three methods seemed to provide similar conditions of the tissue samples. The proportion of cell nuclei: whole cells was 80-90%: 10-20% in all laboratories when the samples were prepared by homogenization using a Downs-loose-type shaft or by the mesh membrane method. The %DNA in tail were comparable in both samples among the negative control groups (single oral administration with physiological saline) of all laboratories, and showed an equal degree of increase in both samples of the ethyl methanesulfonate groups (single oral administration at 250 mg/kg) in all laboratories. In conclusion, the homogenization method using a loosely customized Potter-type shaft or a Downs-loose-type shaft, and the mesh membrane method would be equally acceptable for the *in vivo* rodent alkaline Comet assay.

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***In vitro* clastogenicity and phototoxicity of fullerene (C_{60}) nanomaterials in mammalian cells**

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Mutation Research, 2012; **749(1-2)**: 97-100

Carbon nanomaterials such as carbon nanotubes, graphene, and fullerenes (C_{60}) are widely used in industry. Because of human health concerns, their toxic potential has been examined *in vivo* and *in vitro*. Here we used mammalian cells to examine the *in vitro* clastogenicity as well as the phototoxicity of C_{60}. While C_{60} induced no structural chromosome aberrations in CHL/IU cells at up to 5 mg/mL (the maximum concentration tested), it significantly induced polyploidy at 2.5 and 5 mg/mL with and without metabolic activation. In BALB 3T3 cells, C_{60} showed no phototoxic potential but the anatase form of titanium oxide did. Since insoluble nanomaterials cause polyploidy by blocking cytokinesis rather than by damaging DNA, we concluded that the polyploidy induced by C_{60} in CHL/IU cells was probably due to non-DNA interacting mechanisms.

[1]Division of Genetics and Mutagenesis, National Institute of Health Sciences

食品衛生学

特集「塩及び海水の分析法及び信頼性向上の最近の展開」（解説）食の安全を確保するための外部精度管理
渡辺卓穂
Bulletin of the Society of Sea Water Science, Japan, 2013; **67(1)**: 12-18

動物実験代替法

第16章コロニー形成法による細胞毒性試験（第十六改正日本薬局方；一般試験法「7.02医薬品容器試験法」）
(ISO10993-5 : Biological Evaluation of Medical Device – Part 5 : Tests for *In Vitro* Cytotoxicity)
渡辺美香
動物実験代替安全性試験プロトコル集　シーエムシー出版, 東京 (2012) pp. 198-210

医療機器

Biological evaluation and regulation of medical devices in Japan
Kohichi KOJIMA
Biocompatibility and Performance of Medical Devices, Woodhead Publishing Ltd., Cambridge, UK (2012), pp. 404-448

In Japan, unified guidelines for biological safety tests of medical devices have been implemented since 1995. Since then, there have been no marked changes in the basic way of thinking. In recent years, Japan's way of thinking has been introduced into various parts of the ISO 10993 series, and international understanding has also been promoted. The basic test methods used in Japan do not differ from those used outside Japan for most test items. However, there is a perception gap in sample preparation applied to these tests. In Japan, the basic stance is to eliminate all risks systematically. This stance is especially prominent in cytotoxicity tests, sensitization tests and genotoxicity tests. In addition, there is a perception gap also in classification. Focusing on these points, this chapter outlines the Japanese guidance for biological safety tests of medical devices.

第2節　医療機器GLPへの対応
小島幸一
世界への薬事申請書の書き方　成功へのバイブル　第9部　医療機器の国内申請・薬事対応を成功させるポイント　第2章　日本国内申請時におけるGXP適合性調査への対応　技術情報協会, 東京 (2012) pp. 1019-1029

発達神経毒性学

Abnormal brain function of the rat neonate in a prenatal 5-bromo-2'-deoxyuridine (BrdU)-induced developmental disorder model
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International Journal of Developmental Neuroscience, 2012; **30(6)**: 507-515

Neonatal brain function was investigated in a prenatal BrdU-induced developmental disorder

model, which has been reported to exhibit behavioral abnormalities such as locomotor hyperactivity, impaired learning and memory, and lower anxiety in offspring. After 1 h home cage deprivation we observed an increase in the number of c-Fos (neuronal activity marker) immunoreactive cells in several brain regions of the olfactory and stress-related areas in normal neonates at 11 days. Next, pregnant rats were exposed to 50 mg/kg of BrdU from gestation days 9-15, and their offspring at 11 days were home-cage deprived. Compared to vehicle control, the number of c-Fos immunoreactive cells in BrdU group was found to be decreased in the piriform cortex and locus coeruleus, which are known to play an important role in neonatal learning and memory. We also analyzed Pearson product-moment correlation coefficient of the number of c-Fos immunoreactive cells, focusing on the piriform cortex and locus coeruleus *versus* numerous other brain areas (11 areas including amygdala). Numerous significant correlations were observed in the vehicle control group, however, correlations of the locus coeruleus disappeared in the BrdU group. By observing c-Fos immunoreactivity after home cage deprivation our study uncovers abnormal brain functions as early as postnatal day 11 in this disorder model. Based on these results, we propose a new histological approach for functional characterization of developmental disorder models.

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Current problems of *in vivo* developmental neurotoxicity tests and a new *in vivo* approach focusing on each step of the developing central nervous system

Makiko KUWAGATA

Congenital Anomalies, 2012; **52(3)**: 129-139

Developmental neurotoxicity (DNT) tests usually focus on postnatal indicators, such as behavior and neuropathology, for the detection of chemically induced neurodevelopmental defects in the central nervous system (CNS). However, low reliability, especially low reproducibility, of behavioral results often causes concern among scientists and the scientific community in general. Guidance of neurohistopathological examination in the DNT guideline also has some shortcomings, especially relating to the methodological aspects. Ongoing international trends in DNT tests have shifted from the use of original *in vivo* animal (mammalian) studies to *in vitro* experiments using cell cultures and/or non-mammalian species, such as fish. *In vitro* systems might initially be useful to screen test chemicals for their DNT potential. Although *in vitro* systems are employed as alternative approaches for DNT studies, the use of *in vivo* studies based on animal models remains an important factor when data are to be extrapolated to the human case. In this review, a new *in vivo* approach that focuses on histopathological observation of each developmental step of the CNS, such as proliferation of neural stem cells, migration of immature neurons, and formation of neural networks, using fetal and neonatal brains after chemical exposure is introduced, and some queries and arguments for current DNT experimental guidelines are discussed.

Chapter 5 Sexual dimorphism in monoamine metabolism in BrdU-treated rats showing behavioral dopamine hypersensitivity: An animal model of schizophrenia

Katsumasa MUNEOKA[1], Makiko KUWAGATA

Sexual Dimorphism, InTech, Rijeka, Croatia (2013) pp. 81-96

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内分泌学

Estrogenic regulation of *Kiss1* mRNA variants in Hatano rats

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Differences in reproductive endocrinology distinguish Hatano high-avoidance animals (HAA) from low-avoidance animals (LAA). Compared to HAA rats, female LAA rats secrete low levels of basal luteinizing hormone (LH) and a reduced LH surge. To investigate the underlying cause of the differences between the two strains, levels of the following mRNAs were measured in the hypothalamus of intact and ovariectomized (OVX) females treated with vehicle control or estradiol-17 β (E2): *gonadotropin-releasing hormone* (*Gnrh*), newly isolated rat kisspeptin (*Kiss*)*1* mRNA variant-1 (*Kiss1*V1) and variant-2 (*Kiss1*V2) and *estrogen receptor* (*Er*)α . In OVX-HAA rats, the levels of *Gnrh* mRNA in the preoptic area (POA) 30 h after E2 treatment were significantly higher than in OVX-LAA rats. For HAA rats, the levels of *Kiss1*V1 and *Kiss1*V2 mRNA in the anteroventral periventricular nucleus (AVPV) were significantly higher in the E2-treated group than in the vehicle-treated group. In the arcuate nucleus (Arc) of HAA rats, *Kiss1*V1 and *Kiss1*V2 expression was significantly lower in E2-treated females compared to vehicle-treated females. *Kiss1*V2 expression was significantly higher than *Kiss1*V1 expression in intact HAA rats. In E2-treated OVX-LAA rats, there were no changes in the expression levels of *Gnrh*, *Kiss1*V1 or *Kiss1*V2. In intact LAA rats, no differences were observed in the expression levels of *Kiss1*V1 or *Kiss1*V2 in the AVPV, but the expression levels of these mRNAs in the Arc were significantly lower in E2-treated OVX-LAA rats. Additionally, no strain differences were observed for *Er*α mRNA expression in either the AVPV or Arc. These results indicate that the failure of estrogenic regulation of GnRH neurons in the POA and of kisspeptin neurons in the AVPV of LAA rats causes low LH secretion and reduced reproductive function.

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分子生物学

オステオカルシン発現モニターマウスの作製とグルコサミンを用いた骨形成評価の一例

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グルコサミン研究, 2012; **8**: 43-50

オステオカルシン(osteocalcin以下, OC)は，骨の非コラーゲン性タンパク質の25%を占めており，骨組織のなかでも骨芽細胞において強く発現している．OCは骨の鉱質形成やカルシウムイオンの恒常性維持に寄与している．また，血清中のOCは骨形成マーカーとして用いられている．本研究では，OCエンハンサー/プロモーター領域とルシフェラーゼ遺伝子をつなぎ，*in vivo*イメージングによりOC発現をモニターできるトランスジェニックマウスを作製し，D-グルコサミン塩酸塩(以下，GlcN)およびN-アセチル-D-グルコサミン(以下，GlcNAc)が骨形成に与える影響を検討した．

実験に先立ち，作製したトランスジェニックマウスがOC発現をモニターできるかどうかをOCの発現を上昇させることが知られている活性型ビタミンDを用いて検討した．OCプロモーター活性が上昇したことから，作製した本マウスは骨形成の評価に利用できることを確認した．

続いて，各種GlcNを用いた検討を行った．GlcNおよびGlcNAcの4日間短期投与(10%水溶液，強制

経口投与）では，OCプロモーター活性に差はなく，骨形成に与える影響は認められなかった．次に，28日間長期投与（0.1％水溶液，混水投与）では，GlcNAcでは変化がなかったものの，GlcNでは投与後1週間からOCプロモーター活性の上昇が認められ，投与終了まで持続した．このことから，GlcNの継続的な摂取は，骨形成能に一定の効果がある可能性が示された．

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***In vivo* determination of vitamin D function using transgenic mice carrying a human osteocalcin luciferase reporter gene**

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Vitamin D is an essential factor for ossification, and its deficiency causes rickets. Osteocalcin, which is a noncollagenous protein found in bone matrix and involved in mineralization and calcium ion homeostasis, is one of the major bone morphogenetic markers and is used in the evaluation of osteoblast maturation and osteogenic activation. We established transgenic mouse line expressing luciferase under the control of a 10-kb osteocalcin enhancer/promoter sequence. Using these transgenic mice, we evaluated the active forms of vitamins D2 and D3 for their bone morphogenetic function by *in vivo* bioluminescence. As the result, strong activity for ossification was observed with 1α ,25-hydroxyvitamin D3. Our mouse system can offer a feasible detection method for assessment of osteogenic activity in the development of functional foods and medicines by noninvasive screening.

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免疫毒性学

免疫毒性研究の温故知新－免疫毒性学会の発足経過と20周年への提言

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抗てんかん薬フェニトイン投与によるSDラット胎児脳発達への影響

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Biological safety evaluation of electrostatic atomized water using tests for genotoxicity and reproductive toxicity

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LabCyte EPI-Model を用いた JIS L 1918 繊維製品の皮膚一次刺激試験
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SIRC-CVS 試験を用いた眼刺激性評価代替法の国際バリデーション研究(I)
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食品機能学

菜種（カノーラ）油摂取が脳卒中易発症高血圧自然発症ラット（SHRSP）の病態悪化を促進する機序

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中期多臓器発癌試験法によるアラキドン酸の発癌プロモーション作用への影響評価

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DSS誘導ラット大腸炎に対するアラキドン酸補給の影響

内藤由紀子[1], 遠藤恒介[1], 紀　旭[1], 馬　嘯[1], 立花滋博, 安藤栄里子, 青木聡子, 永田伴子, 宮澤大介[2], 岩井直温[1]

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発達神経毒性学

バルプロ酸の胎生期曝露により実験動物に誘発される発達神経毒性

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