研究業績

論文等

免疫毒性学

周産期のアレルギー　―周産期の環境と小児アレルギー疾患発症のリスク―　Developmental Immunotoxicology (DIT)

太田　亮, 大沢基保

周産期医学, 2011; **41(5)**: 609-613

Chapter 6 Immune Toxicity 6.1 Concept

Motoyasu OHSAWA

Bioassay and Bio-informatics - for Environmental Assessment and Medical Sciences (Eds. Hideo UTSUMI and Katsuhiko NAKAMURO), Kougaku-Tosho, Pub. Ltd., Tokyo (2011) pp. 125-126

Chapter 6 Immune Toxicity 6.4 *In Vitro* IgM Production Test

Motoyasu OHSAWA, Kazuko TAKAHASHI[1], Hiroshi TOKUNAGA[2]

Bioassay and Bio-informatics - for Environmental Assessment and Medical Sciences (Eds. Hideo UTSUMI and Katsuhiko NAKAMURO), Kougaku-Tosho, Pub. Ltd., Tokyo (2011) pp. 139-145

[1]Faculty of Pharmaceutical Sciences, Teikyo University; [2]Department of Environmental Chemistry, National Institute of Health Sciences

免疫毒性学の課題

小野　宏

ImmunoTox Letter, 2011; **16(1)**: 1-3

実験動物学

Endocrinological differences between Hatano high- and low-avoidance rats during early two-way avoidance acquisition

Sayaka AKIEDA-ASAI[1,2,3], Ryo OHTA, Mariko SHIROTA[4], Sukanya JAROENPORN[5], Gen WATANABE[1,2], Kazuyoshi TAYA[1,2]

Experimental Animals, 2011; **60(5)**: 509-516

Hatano high (HAA)- and low (LAA)-avoidance rats were selected from Sprague-Dawley rats genetically on the basis of their active avoidance behavior in a shuttle-box test. The purpose of this study was to investigate stress-related alterations of hormones corticotropin-releasing hormone (CRH), arginine-vasopressin (AVP), prolactin, and adrenocorticotropin (ACTH) in the brain and blood during early avoidance acquisition using two lines of Hatano rats. In paraventricular nucleus (PVN) of the hypothalamus, the CRH levels in HAA rats were significantly increased after shuttle-box tasks compared with before the tasks, whereas the CRH levels in LAA rats

significantly decreased after shuttle-box tasks compared with before the tasks. In the HAA rats, the CRH and AVP levels in the median eminence decreased after shuttle-box tasks, whereas there were no significant differences in the levels between before and after shuttle-box tasks in LAA rats. The plasma concentrations of ACTH were significantly higher in HAA rats than in LAA rats after shuttle-box tasks. These results show that the response of CRH-ACTH was higher in HAA rats than in LAA rats. This phenotype may be an important reason for the high avoidance rates of shuttle-box tasks in HAA rats. These endocrine differences in early avoidance acquisition may be involved in regulation of their avoidance responses in the shuttle-box task.

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毒性病理学

クリューバー・バレラ染色におけるコントロールサーベイ報告

小林良光[1], 中野健二[2], 山口　肇, 打屋尚章[3], 古川文夫[4], 阿部　寛[5], 葛西久芳[2], 福田種男[6], 尾崎善孝[7]

実験病理組織技術研究会誌, 2011; **20(1)**: 1-42

[1]順天堂大学医学部第二解剖講座; [2]アステラスリサーチテクノロジー株式会社; [3]国立がんセンター研究所; [4]株式会社DIMS医科学研究所; [5]順天堂大学医学部病理学第一講座; [6]株式会社サンプラネット安全性研究ユニット; [7]株式会社江東微生物研究所

一般毒性学

臨床検査

高島宏昌

安全性試験の教育・研修テキスト(基礎編)第4版, 安全性試験受託研究機関協議会(2011) pp. 103-130

生殖・発生毒性学

An attempt to cell differentiation in three-dimensional culture system using non-feeder ES-D3 cells and feeder layer type ES cells

Koichi IMAI[1], Shoji TAKEDA[1], Akito TANOUE[2], Kazuaki NAKAMURA[2], Kazuhiko SUESE[3], Fumio WATARI[4], Hiromasa TAKASHIMA

Journal of Oral Tissue Engineering, 2011; **8(3)**: 203-211

The embryonic stem cell test (EST) is an *in vitro* assay that has been developed to assess the embryotoxic potential of chemicals and biomaterials. An attempt for improvement in that ES cells used in the EST protocol are restricted to ES-D3 cells. If other kinds of ES cell become available, its experimental application will be further usefulness. We compared the incidence of pulsation between ES-D3 cells requiring no feeder cells for cultivation and EL M3 cells or ES-R1-EGFP B2/EGFP cells requiring feeder cells, to explore the experimental possibility of using ES cells requiring feeder cells.

As the present results with ES-D3 and EL M3 cells were similar to those obtained under the two-dimensional condition, these two kinds of cell are thought to be equally available under the present three-dimensional conditions. On the other hand, because ES-R1-EGFP B2/EGFP cells did not show any pulsation at all in the three-dimensional culture, other experimental conditions for the three-dimensional culture method need to be established with those cells. Besides, it was suggested that similar results could be obtained with EL M3 cells requiring feeder cells for cultivation compared to those with ES-D3 cells.

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細胞毒性学

平成21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3報）—細胞毒性試験法の検討—

柘植英哉[1], 森　充生[1], 大庭澄明[1], 大内　正[1], 寺田三郎[1], 五島隆志[2], 田邊豊重[2], 山影康次, 田中憲穂, 渡辺美香, 畔上二郎, 大向英夫, 小島　肇[3]

医薬品医療機器レギュラトリーサイエンス, 2011; **42(3)**: 258-271

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An international validation study of a Bhas 42 cell transformation assay for the prediction of chemical carcinogenicity

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Mutation Research, 2011; **725(1-2)**: 57-77

The Bhas 42 cell transformation assay is a sensitive short-term system for predicting chemical carcinogenicity. Bhas 42 cells were established from BALB/c 3T3 cells by the transfection of v-Ha-*ras* gene and postulated to have acquired an initiated state in the two-stage carcinogenesis theory. The Bhas 42 cell transformation assay is capable of detecting both tumor-initiating and tumor-promoting activities of chemical carcinogens. The full assay protocol consists of two components, the initiation assay and the promotion assay, to detect the initiating activity and the promoting activity, respectively. An international study was carried out to validate this cell transformation assay in which six laboratories from three countries participated. Twelve coded chemicals were examined in total and each chemical was tested by three laboratories. In the initiation assay, concordant results were obtained by three laboratories for eight out of ten chemicals and in the promotion assay, concordant results were achieved for ten of twelve chemicals. The positive results were obtained in all three laboratories with the following chemicals: 2-acetylaminofluorene was positive in both initiation and promotion assays; dibenz[*a*,*h*]anthracene was positive in the initiation assay; sodium arsenite, lithocholic acid, cadmium chloride, mezerein and methapyrilene hydrochloride were positive in the promotion assay. *o*-Toluidine hydrochloride was positive in the both assays in

two of the three laboratories. D-Mannitol, caffeine and L-ascorbic acid were negative in both assays in all the laboratories, and anthracene was negative in both assays in two of the three laboratories except one laboratory obtaining positive result in the promotion assay. Consequently, the Bhas 42 cell transformation assay correctly discriminated all six carcinogens and two tumor promoters from four non-carcinogens. Thus, the present study demonstrated that the Bhas 42 cell transformation assay is transferable and reproducible between laboratories and applicable to the prediction of chemical carcinogenicity. In addition, by comparison of the present results with intra-laboratory data previously published, within-laboratory reproducibility using the Bhas 42 cell transformation assay was also confirmed.

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A method for selecting mammal transformed cells

Kiyoshi SASAKI

European Patent Specification, EP 2 163 895 B1 (2011)

第10章　癌原性試験の実験手法　第2節　形質転換試験

田中憲穂, 佐々木澄志

「最新　動物実験代替法の技法ノウハウ」, (株)技術情報協会, 東京(2011)pp. 228-241

Cell transformation assays for prediction of carcinogenic potential: state of the science and future research needs

Stuart CRETON[1], Marilyn AARDEMA[2], Paul L. CARMICHAEL[3], James S. HARVEY[4], Francis L. MARTIN[5], Robert F. NEWBOLD[6], Michael R. O'DONOVAN[7], Kamala PANT[8], Albrecht POTH[9], Ayako SAKAI, Kiyoshi SASAKI, Andrew D. SCOTT[3], Leonard M. SCHECHTMAN[10], Phine R. SHEN[11], Noriho TANAKA, Hemad YASAEI[6]

Mutagenesis, 2012; **27(1)**: 93-101

Cell transformation assays (CTAs) have long been proposed as *in vitro* methods for the identification of potential chemical carcinogens. Despite showing good correlation with rodent bioassay data, concerns over the subjective nature of using morphological criteria for identifying transformed cells and a lack of understanding of the mechanistic basis of the assays has limited their acceptance for regulatory purposes. However, recent drivers to find alternative carcinogenicity assessment methodologies, such as the Seventh Amendment to the EU Cosmetics Directive, have fuelled renewed interest in CTAs. Research is currently ongoing to improve the objectivity of the assays, reveal the underlying molecular changes leading to transformation and explore the use of novel cell types. The UK NC3Rs held an international workshop in November 2010 to review the current state of the art in this field and provide directions for future research. This paper outlines the key points highlighted at this meeting.

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Genetics and Pharmacogenomics, Brunel University; [7]AstraZeneca R&D; [8]Bioreliance Corporation; [9]Harlan Cytotest Cell Research GmbH; [10]Innovative Toxicology Consulting; [11]Department of Medical Oncology, Dana Farber Cancer Institute

遺伝毒性学

Use of the *in vivo* skin comet assay to evaluate the DNA-damaging potential of chemicals applied to the skin

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Mutation Research, 2011; **726(2)**: 175-180

The aim of the present study was to evaluate both sensitivity and specificity of an *in vivo* skin comet assay using chemically treated, hairless mouse dorsal skin as a model. *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG, 0.0125–0.2%), 4-nitroquinoline-1-oxide (4NQO, 0.01–0.25%), mitomycin C (MMC, 0.0125–0.05%), benzo[a]pyrene (B[a]P, 0.25–2%), and 7,12-dimethylbenz[a]anthracene (DMBA, 0.25–1%) were each applied once to the dorsal skin of hairless male mice; after 3 h, epidermal skin cells were isolated, and the alkaline comet assay was performed. The assay was performed after 24 h for only the B[a]P and DMBA. Furthermore, B[a]P and DMBA were evaluated by alkaline comet assay using liver cells after both 3 and 24 h.

The mean percent of DNA (%DNA) in tail in the 0.05–0.2% MNNG and 0.1–0.25% 4NQO treatment groups was markedly higher than in the control group at 3 h post-application. Although the mean %DNA values in the tail in the B[a]P and DMBA groups were the same as the controls at 3 h post-application, the 2% B[a]P and 1% DMBA groups showed significantly higher values versus controls 24 h after application. No significant increases in the mean %DNA in the tail were observed in the MMC group. No clear increases in %DNA in the tail were observed in the B[a]P and DMBA groups at 3 or 24 h after application in the liver.

These results suggest that the *in vivo* skin comet assay is able to accurately identify DNA-damaging potential with a skin-specific response and is a useful method to detect the DNA-damaging potential of genotoxic chemicals on the skin.

Usefulness of combined *in vivo* skin comet assay and *in vivo* skin micronucleus test

Tomoyasu TOYOIZUMI, Ryo OHTA, Kumiko KAWAKAMI, Yuzuki NAKAGAWA, Yoshiyuki TAZURA, Makiko KUWAGATA, Satoshi NOGUCHI, Hajime SUI, Kohji YAMAKAGE

Mutation Research, 2012; **743(1-2)**: 42-51

We have already found that the *in vivo* skin comet assay is useful for the evaluation of primary DNA damage induced by genotoxic chemicals in epidermal skin cells. The aim of the present study was to evaluate the sensitivity and specificity of the combined *in vivo* skin comet assay and *in vivo* skin micronucleus (MN) test using the same animal to explore the usefulness of the new test method.

The combined alkaline comet assay and MN test was carried out with three chemicals: 4-nitroquinoline-1-oxide (4NQO), *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) and benzo[a]pyrene (B[a]P). In the first experiment, we compared DNA- and chromosome-damaging effects of 3 [72, 24 and 3 hours (h) before sacrifice] and 4 applications (72, 48, 24 and 3 h before sacrifice) of 4NQO, which induces dermal irritancy. The animals were euthanized and their skin was sampled

for the combination test. As a result, the 4-application method was able to detect both DNA- and chromosome-damaging potential with a lower concentration; therefore, in the second experiment, MNNG and B[a]P were topically applied four times, respectively. The animals were euthanized, and then their skins were sampled for combination tests. In the alkaline comet assay, significant differences in the percent of DNA (%DNA) in the tail were observed in epidermal skin cells treated with MNNG and B[a]P. In the MN test, an increased frequency of MN cells (%MN) cells was observed by treatment with MNNG; however, there were no significant increases. In contrast, significant differences in %MN were observed by treatment with B[a]P.

From these results, we conclude that the combined *in vivo* skin comet assay and *in vivo* MN test was useful because it can detect different genotoxicity with the same sampling time and reduce the number of animals used.

Evaluation of *in vivo* mutagenicity by 2,4-diaminotoluene and 2,6-diaminotoluene in liver of F344 *gpt* delta transgenic rat dosed for 28 days: A collaborative study of the *gpt* delta transgenic rat mutation assay

Hajime SUI, Ryo OHTA, Toshiyuki SHIRAGIKU[1], Ayaka AKAHORI[2], Kenichiro SUZUKI[2], Madoka NAKAJIMA[2], Hiroyuki HAYASHI[3], Kenichi MASUMURA[4], Takehiko NOHMI[4]

Genes and Environment, 2012; **34(1)**: 25-33

The transgenic rodent (TGR) assay has been widely used to study *in vivo* gene mutations by chemicals or radiation; however, an optimal protocol has not yet been established to assess unknown genotoxic potential. The International Workshop on Genotoxicity Testing (IWGT) strongly recommends a repeated-dose regimen for the TGR assay protocol for regulatory safety assessment as follows: a treatment period of 28 days and a sampling time of 3 days following the final treatment. In this study, TGR assays using F344 *gpt* delta transgenic rats were conducted at three laboratories to evaluate the validity of the IWGT protocol, as part of a collaborative study of the transgenic rat mutation assay. Male F344 *gpt* delta transgenic rats were orally treated with 2,4-diaminotoluene (2,4-DAT; hepatic carcinogen in rodents; 10 and 30 mg/kg/day) or 2,6-diaminotoluene (2,6-DAT; non-carcinogen in rodents; 60 mg/kg/day) once daily for 28 days. Rats were euthanized 3 days after the last dosing, and then mutant frequencies (MFs) of the *gpt* gene in the livers were studied. As a result, a significant increase in the MF was observed at 30 mg/kg in the 2,4-DAT-treated group, but not in the 2,6-DAT-treated group. These results were commonly observed among the three laboratories. In addition, the overall results from the three laboratories were in general agreement. These results indicate that 2,4-DAT induces gene mutation in the liver of *gpt* delta rats, but 2,6-DAT does not. These results also indicate that the F344 *gpt* delta transgenic rat mutation assay can distinguish differences in the *in vivo* mutagenic potential between a hepatic carcinogen and a non-carcinogen. Results from one laboratory showed more variability than those from the other two laboratories, and this appearance was due to the smaller number of colonies scored. Thus, these results demonstrate that the IWGT protocol for the TGR assays is valid, and show that consistent results are obtained among different laboratories.

[1]Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd.; [2]Biosafety Research Center, Foods, Drugs and Pesticides; [3]Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd.; [4]Division of Genetics and Mutagenesis, National Institute of Health Sciences

環境衛生学

Nasal instillation of nanoparticle-rich diesel exhaust particles slightly affects emotional behavior and learning capability in rats

Syunji YOKOTA, Hiromasa TAKASHIMA, Ryo OHTA, Yoshiaki SAITO, Takashi MIYAHARA, Yuka YOSHIDA, Tsukasa NEGURA, Mika SENUMA, Kenji USUMI, Naoyuki HIRABAYASHI, Takaho WATANABE, Shinji HORIUCHI, Yuji FUJITANI[1], Seishiro HIRANO[1], Hidekazu FUJIMAKI[1]

Journal of Toxicological Sciences, 2011; **36(3)**: 267-276

In the present study, in order to reveal novel adverse effects of ultrafine particles (UFP) on the central nervous system, the effects of nanoparticle-rich diesel exhaust particles (NRDEP; count mode diameter, 21.45 nm) on emotional behavior, learning capability and brain neurotransmitter levels were studied in rats by intranasal instillation (iNI). NRDEP (10 and 50 μg/rat) was instilled into 2-week old infant, male rats once a week for 4 weeks. Spontaneous motor activity measured was observed to be inverse to the dose level. In active avoidance tests using a shuttle box, NRDEP-treated animals showed a lower avoidance performance than control animals given air-instillation. The levels of dopamine and its metabolite (DOPAC) in the medial mammillary nucleus of the brain tended to be lower in the NRDEP-treated animals. From these results, although the effects of NRDEP by iNI on the emotionality and the brain neurotransmitter levels were not fully clear, the results obtained by avoidance testing suggested involvement of UFP in learning capability.

[1]Research Center for Environmental Risk, National Institute for Environmental Studies

第11章　職業病とその予防

大沢基保

保健と環境（日本薬学会編）第2版, 東京化学同人, 東京 (2011) pp. 246-251

食品衛生学

重金属検査の食品衛生外部精度管理調査

渡辺卓穂, 高坂典子, 勝村利恵子, 福光　徹, 鈴木達也, 大島赴夫

食品衛生研究, 2011; **61(4)**: 15-22

講座　シリーズ企画「不確かさ―食品分析精度を維持，向上するために（3）―」　外部精度管理調査結果からみた食品分析精度

渡辺卓穂

食品衛生学雑誌, 2011; **52(5)**: J-315-J-322

動物実験代替法

代替法の定義・用語集（巻末付録）

小野　宏, 小島　肇[1]

「最新　動物実験代替法の技法ノウハウ」, (株)技術情報協会, 東京 (2011) pp. 367-388

[1]国立医薬品食品衛生研究所

第7章　急性毒性試験の実験手技
渡辺美香
「最新　動物実験代替法の技法ノウハウ」, (株)技術情報協会, 東京(2011) pp. 149-167

刺激性試験

刺激性試験
小島幸一
安全性試験の教育・研修テキスト(基礎編)第4版, 安全性試験受託研究機関協議会(2011) pp. 265-282

医療機器

医療機器、医用材料の生物学的安全性評価試験
小島幸一
医療材料 [外科製品・生体材料] の臨床ニーズ集, (株)技術情報協会, 東京(2011) pp. 260-298

発達神経毒性学

Effects of the genotoxic agent 5-bromo-2'-deoxyuridine with or without pre-pubertal gonadectomy on brain monoamines and their metabolites in female rats
Makiko KUWAGATA, Katsumasa MUNEOKA[1], Tetsuo OGAWA[1], Seiji SHIODA[1]
Brain Research Bulletin, 2011; **85(3-4)**: 207-211

A nucleotide analog 5-bromo-2′-deoxyuridine (BrdU) is a genotoxic compound. Previous studies have demonstrated that prenatal treatment of rodents with BrdU affects the development of cortical neurons, reduces dopamine levels, and elevates serotonin (5-HT) levels in the striatum in adult male offspring from BrdU-treated dams. Moreover, prenatal BrdU-treated rats show locomotor hyperactivity in both males and females. This study investigated sexual dimorphism in the effect of prenatal BrdU on monoamine metabolism. Sprague–Dawley rats were treated with BrdU on gestational days 9–15 (50 mg/kg, *i.p.*) and monoamine metabolism was examined in female rats at 10 weeks of age. The influence of pre-pubertal gonadectomy on the effects of BrdU was also investigated. BrdU-treated females showed elevations of dopamine and 5-HT levels in the striatum; reductions in dopamine, dihydroxyphenylacetic acid, or homovanillic acid (HVA) in the hypothalamus or the midbrain; and elevated HVA and 5-HT in the hippocampus. Pre-pubertal gonadectomy had a suppressive effect on striatal dopamine levels in prenatal BrdU-treated females. The present data indicate sexual dimorphic effects of prenatal BrdU-treatment in striatal dopamine metabolism but not in serotonergic metabolism and suggest a contribution of the increasing gonadal hormones that accompany puberty to this sex difference.

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Hyperactivity induced by prenatal BrdU exposure across several experimental conditions
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Congenital Anomalies, 2011; **51(4)**: 177-182

Behavioral results are sometimes not reproducible even in the positive controls of developmental neurotoxicity (DNT) tests. Effects of several factors on the results should be considered. In the present paper, we examined the effects of strain-, gender-, and test-condition differences on BrdU-

induced hyperactivity. The results showed that BrdU-induced hyperactivity was reproducible in two rat strains (SD and F344 rats), rodent species (rat and mouse), and both sexes. When the level of background sound in a test room was increased, the hyperactivity was persistent, resulting in no effect of background sound on BrdU-induced hyperactivity. Thus, we have demonstrated that the BrdU-animal model is a useful positive control via prenatal exposure to validate the entire DNT test process.

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内分泌学

Endocrine mechanisms responsible for different follicular development during the estrous cycle in Hatano high- and low-avoidance rats

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Journal of Reproduction and Development, 2011; **57(6)**: 690-699

Hatano high- and low-avoidance rats (HAA and LAA strains, respectively) were selected and bred according to the avoidance rate in a shuttle-box task. Although they have clear strain differences in ovarian function, their endocrine mechanisms still remain to be clarified. Differences in female reproductive endocrinology between the strains were investigated by means of measuring the plasma concentration of reproductive hormones during the estrous cycle. LAA rats showed approximately threefold lower basal and surge levels of LH, a more than fourfold lower level of FSH surges and higher levels of inhibin A and inhibin B during the estrous cycle compared with the levels seen in HAA rats. The concentration of estradiol-17 β in the proestrous stage was significantly lower in LAA rats than in HAA rats. Additionally, LH and FSH secretions from primary cultured anterior pituitary cells with or without *in vitro* GnRH stimulation were lower in the cells derived from LAA rats and, in terms of FSH secretion, were unresponsive to GnRH in contrast to cells derived from HAA rats. Although an increased number of preantral follicles in diestrus were observed in LAA rats, number of hCG-induced ovulation was lower in LAA rats. LAA rats may have much more follicle growth during the early stage of folliculogenesis, but most follicles might not grow into mature follicles. These results strongly suggest that the strain difference in ovarian function of these two Hatano rats is due to the difference in the regulation of hypothalamo-hypophyseal system for gonadotropins secretion.

[1]Primate Research Unit, Department of Biology, Faculty of Science, Chulalongkorn University; [2]Department of Basic Veterinary Science, The United Graduate School of Veterinary Sciences, Gifu University; [3]Laboratory of Veterinary Physiology, Department of Veterinary Medicine, Faculty of Agriculture, Tokyo University of Agriculture and Technology; [4]Frontier Science Research Center, University of Miyazaki; [5]Laboratory of Comparative Toxicology, School of Veterinary Medicine, Azabu University

発生学

Distribution of the longevity gene product, SIRT1, in developing mouse organs

Tetsuo OGAWA[1,2], Chizu WAKAI[2], Tomomi SAITO[1], Aya MURAYAMA[1], Yuuichi MIMURA[2], Sachiko YOUFU[1,2], Tomoya NAKAMACHI[2], Makiko KUWAGATA, Kazue SATOH[1,2], Seiji SHIODA[1,2]

Congenital Anomalies, 2011; **51(2)**: 70-79

A longevity gene product, Sir2 (silent information regulator 2) is a NAD-dependent histone deacetylase involved in longevity in yeasts, worms and flies. The mammalian homolog of Sir2, SIRT1 (sirtuin 1), has been shown to play important roles related to anti-aging effects (regulating apoptosis, stress tolerance, insulin resistance, and fat metabolism). Recently, SIRT1 expression has been demonstrated to occur at as early as embryonic day 10.5 in mice. SIRT1 during developing period may be involved in the mechanism of developmental origins of adult diseases, such as diabetes and cardiovascular disease. To investigate the contribution of SIRT1, it is important to reveal the distribution of this protein during development. In the present study, we demonstrated the distribution of immunoreactivity of SIRT1 in mouse organs during prenatal and neonatal development by staining a wide variety of serial sections. The SIRT1 immunoreactivity was strongly observed in the neuroepithelial layer, dorsal root ganglion, trigeminal ganglion, eyes, roots of whiskers, and internal organs, including the testis, liver, heart, kidney, and lung during the fetal period. Neurons which had finished migrating still showed relatively strong immunoreactivity. The immunoreactivity was completely absorbed by the blocking peptide in an absorption test. During the postnatal period, the immunoreactivities in most of these organs, except the heart and testis weakened, with the liver most dramatically affected. As SIRT1 expression was demonstrated in a wide variety of developing organs, further study to investigate prenatal factors which affect SIRT1 expression and its activity is important.

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The complete control of murine pregnancy from embryo implantation to parturition

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Reproduction, 2012; **143(3)**: 411-415

The ovary is the main secretory source of progestin and estrogen and is indispensable to the maintenance of all events of pregnancy in mice. The purpose of this study was to control all processes of pregnancy in mice, from embryo implantation to parturition, without ovaries. The ovaries were removed before embryo implantation, and a single injection of medroxyprogesterone acetate (MPA) was given. Embryo implantation was induced by leukemia inhibitory factor, which can substitute 17 β -estradiol (E_2). Continuous exposure to E_2 was necessary at mid-pregnancy, when placentation was completed. All mice sustained pregnancy without ovaries before parturition, which was initiated by the removal of E_2 and MPA. Murine pregnancy is a complicated process involving embryo implantation, placentation, and parturition. Complete control of pregnancy was achieved with the simple treatment of MPA and E_2 after induction of embryo implantation. Here, time-dependent events in the uterus during pregnancy could be realized without the ovaries, because the initiation of each event could be stringently controlled by hormonal treatments.

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化学・生化学

植物油脂長期投与によるミニブタ組織のステロイドホルモンへの影響

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免疫毒性学

h-CLATによる化学物質の感作性検出のための基礎検討

藤田恵子, 渡辺美香, 小林美和子, 奥富弘子, 新藤智子

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香取輝美, 新藤智子, 大沢基保, 小島幸一, 手島玲子[1]

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Influence of *in vitro* angiogenesis by ultrafine titanium dioxide and zinc oxide

Koichi IMAI[1], Tetsunari NISHIKAWA[2], Akio TANAKA[1], Fumio WATARI[3], Hiromasa TAKASHIMA, Shoji TAKEDA[1]

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生殖・発生毒性学

母動物へのペントバルビタール投与による胎児の麻酔状態に関する検討

瀬沼美華, 吉田由香, 桑形麻樹子, 折戸謙介[1], 今井弘一[2], 高島宏昌, 小島幸一

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ラット胎生期ヒ素曝露の胎児脳発達への影響

瀬沼美華, 古谷真美, 高島宏昌, 太田　亮, 小川哲郎[1,2], 桑形麻樹子

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Investigation about anesthesia of rodent fetuses with transplacental pentobarbital administration

Mika SENUMA, Hiromasa TAKASHIMA, Makiko KUWAGATA, Yuka YOSHIDA, Koichi IMAI[1]

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[1]Osaka Dental University

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Koichi IMAI[1], Shoji TAKEDA[1], Akito TANOUE[2], Mika SENUMA, Hiromasa TAKASHIMA

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鈴木紀之[1], 小関直輝[2], 山田　徹[2], 木村　裕[3], 相場節也[3], 豊泉友康, 渡辺美香, 太田　亮, 斎藤幸一[1]

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帯電微粒子水のSDラットを用いた生殖発生毒性の評価

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細胞毒性学

A validation study on a Bhas 42 cell transformation assay using 96-well micro-plates

Ayako SAKAI, Shoko ARAI, Kiyoshi SASAKI, Dai MURAMATSU, Nobuko ENDOU, Fukutaro MIZUHASHI[1], Sawako KASAMOTO[1], Miho NAGAI[1], Maiko TAKAI[1], Masumi ASAKURA[2], Nobuhiko TASHIRO[3], Nana ISHII[3], Shojiro YAMAZAKI, Makoto UMEDA, Noriho TANAKA
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Kiyoshi SASAKI, Dai MURAMATSU, Shoko ARAI, Nobuko ENDOU, Ayako SAKAI, Shojiro YAMAZAKI, Makoto UMEDA, Noriho TANAKA
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環境エピゲノミクスによる化学物質の経世代影響と進化への可能性
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ヒト3次元培養表皮モデルを用いた皮膚刺激性試験による低刺激性物質検出法の検討
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Hajime KOJIMA[1], Kohji YAMAKAGE, Sumiaki OBA[2], Hideya TSUGE[2], Mitsuo AOKI[3]
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食品機能学

ミニブタ組織のステロイドホルモンに対する植物油脂長期投与の影響

宮澤大介[1], 大原直樹[1], 桜井　杏[1], 安井裕子[1], 北森一哉[1], 斉藤義明, 臼見憲司, 山田和代[1], 今井　唯[1], 山田英里[1], 大橋彩乃[1], 水谷友香[1], 野々垣常正[1], 小林身哉[1], 奥山治美[1]

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アラキドン酸のラットにおける中期多臓器発癌試験

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脳卒中易発症高血圧自然発症ラット(SHRSP)を用いるアラキドン酸の病態進行に対する影響の検討

青木聡子, 立花滋博, 安藤栄里子, 田面喜之, 古谷真美, 永田伴子, 内藤由紀子[1], 大原直樹[2]

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薬物誘導大腸炎モデルラットにおけるアラキドン酸補給の影響

内藤由紀子[1], 立花滋博, 安藤栄里子, 青木聡子, 古谷真美, 田面喜之, 永田伴子, 岩井直温[1]

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Yukiko NAITO[1], Shigehiro TACHIBANA, Eriko ANDO, Mami FURUYA, Tomoko NAGATA, Xu JI[1], Xiao MA[1], Kosuke ENDO[1], Naoharu IWAI[1]

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Makiko KUWAGATA

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Searching Gene candidates responsible for risk of mental disorders in the mouse intrauterine undernutrition model

Tetsuo OGAWA[1], Randeep RAKWAL[1], Junko SHIBATO[1], Tomomi SAITO[1], Aya MURAYAMA[1], Gaku TAMURA[1], Makiko KUWAGATA, Seiji SHIODA[1]

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Sodium (meta) arsenite exposure effects on the early developing rat fetal brain: A morpho-histopathological examination

Makiko KUWAGATA, Mika SENUMA, Mami FURUYA, Hiromasa TAKASHIMA, Tetsuo OGAWA[1], Seiji SHIODA[1]

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Quality Assurance for biotechnology-derived pharmaceuticals in preclinical safety evaluation

Toshiki UMETANI[1], JSQA GLP Division, Study Group1, Subgroup1, Team B (including Kazuyoshi WADA)

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View exchange toward resolution of various problems by oneself -Various trials for the communication among members-

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Key considerations for defining the electronic data as raw data in Japanese pharmaceuticals

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