研究業績

論文等

実験動物学

Effects of transmaternal exposure to genistein in Hatano high- and low-avoidance rats

Ryo OHTA, Mariko SHIROTA, Yukiko KANAZAWA, Tomoko SHINDO, Mami FURUYA, Takayuki SEKI, Hiroshi ONO, Kohichi KOJIMA, Sayaka ASAI[1], Gen WATANABE[1], Kazuyoshi TAYA[1]

Experimental Animals, 2009; **58(5)**: 471-479

Hatano high- and low-avoidance (HAA and LAA) rats are separated by breeding from Sprague-Dawley rats by high versus low rates of avoidance responses in a shuttle-box task. In addition, compared to HAA rats, LAA rats show lower running-wheel activity, later sexual maturation, 5-day estrous cycling, lower sperm motility, more pronounced immunological reactions, and are generally less reactive to stress. The present study was designed to compare the effects of transmaternal exposure to genistein on these characteristics between HAA and LAA rats. To this aim, litters from both strains were fostered onto Sprague-Dawley rats receiving genistein by gavage with 5 mg/animal/day from day 17 of pregnancy through day 21 of lactation. Inhibited growth after weaning and reduced uterine weight at weaning were observed in the LAA offspring reared by genistein-treated dams. IgM antibody production in response to sheep red blood cells was significantly decreased in the HAA offspring reared by genistein-treated dams. During restraint stress, the plasma concentration of corticosterone was significantly lower in the LAA offspring reared by genistein-treated dams. Strain-related differences were detected in shuttle-box avoidance performance, running-wheel activity, estrous cycling, and sperm motility. The results demonstrate that transmaternal exposure to genistein potentially affects the immunological and stress responses as well as the post-weaning growth of the offspring. It suggests that a comparative study using Hatano rats would be useful for studying the influence of endocrine active chemicals on the whole body systems.

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技術指導員の活動と役割

畔上二郎

LABIO21, 2010; **39**: 10-11

毒性病理学

Early embryonic losses in mice induced by diethylstilbestrol

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Congenital Anomalies, 2009; **49(4)**: 269-273

Estrogens cause embryonic lethality and the disturbance of early placental development in mice. Diethylstilbestrol (DES) at 1, 10, or 100 μg/kg was orally administered to Institute of Cancer Research mice on gestational days (GD) 4 through 8, and the uterus and placenta were examined

histopathologically on GD 9. Decidua of DES-treated mice showed insufficient development, and the uterine lumen at the implantation site did not effectively minimize. The trophoblast giant cell layer was not separated from the uterine lumen by the decidua capsularis, and hemorrhage from the denuded trophoblast giant cell layer into the uterine lumen was noted at the peripheral part of the decidua basalis. The results of the present study suggest that decidual hypoplasia and subsequent placental hemorrhage causes fetal death due to the administration of DES during the early stage of pregnancy.

[1]Department of Life Science, Kinki University

一般毒性学

Safety assessment of *Lactobacillus brevis* KB290 as a probiotic strain

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Food and Chemical Toxicology, 2009; **47(10)**: 2450-2453

Lactobacillus brevis KB290 (KB290), a plant-derived probiotic lactic acid bacterium, reportedly improves gut health and stimulates immune function. Here we extensively investigated the geno-, acute, subacute, and subchronic toxicity of KB290 and its bacterial translocation potential. KB290 was non-mutagenic in the bacterial reverse mutation assay by the preincubation method. In the single oral dose toxicity test, KB290 at $\geq 10^9$ cfu/mL was nontoxic at maximum capacity (20 mL/kg). When 10^8, 10^9, or 10^{10} cfu/kg was administered daily to rats by gavage for 2 weeks (subacute assay), we observed no clear treatment-related effect and no evidence of bacterial translocation from the gastrointestinal tract. When it was administered for 13 weeks (subchronic assay), we again observed no clear treatment-related effect and no significant toxicological effect. Based on those results, we consider 10^{10} cfu/kg per day, the highest dose tested, to be the no observed adverse effect level (NOAEL). These results suggest that KB290 is safe for human consumption.

[1]Research Institute, Kagome Co., Ltd.; [2]Huntingdon Research Centre, Huntingdon Life Sciences Ltd.

Attenuation of cisplatin nephrotoxicity by inhibition of soluble epoxide hydrolase

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Cell Biology and Toxicology, 2009; **25(3)**: 217-225

Cisplatin is a highly effective chemotherapeutic agent against many tumors; however, it is also a potent nephrotoxicant. Given that there have been no significant advances in our ability to clinically manage acute renal failure since the advent of dialysis, the development of novel strategies to ablate nephrotoxicity would represent a significant development. In this study, we investigated the ability of an inhibitor of soluble epoxide hydrolase (sEH), *n*-butyl ester of 12-(3-adamantan-1-yl-ureiido)-dodecanoic acid (nbAUDA), to attenuate cisplatin-induced nephrotoxicity. nbAUDA is quickly converted to AUDA and results in maintenance of high AUDA levels *in vivo*. Subcutaneous administration of 40 mg/kg of nbAUDA to C3H mice every 24 h resulted in elevated blood levels of AUDA; this protocol was also associated with attenuation of nephrotoxicity induced by cisplatin (intraperitoneal injection) as assessed by BUN levels and histological evaluation of kidneys. This is the first report of the use of sEH inhibitors to protect against acute nephrotoxicity and suggests a therapeutic potential of these compounds.

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Health Science Center; [2]Department of Veterinary Integrated Biosciences, College of Veterinary Medicine, Texas A&M University; [3]Department of Entomology and UCD Cancer Center, University of California at Davis

細胞毒性学

Comparison of sensitivity to arsenic compounds between a Bhas 42 cell transformation assay and a BALB/c 3T3 cell transformation assay

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Mutation Research, 2009; 675(1-2): 66-70

A short-term cell transformation assay has recently been developed, using Bhas 42 cells which were established from BALB/c 3T3 cells transfected by v-Ha-*ras* gene and postulated to be initiated in the two-stage carcinogenesis theory. The Bhas 42 cell transformation assay has been reported to be capable of detecting initiating and promoting activities of chemical carcinogens, according to the different protocols, initiation assay and promotion assay, respectively. The assay is superior to classical transformation assays in cost and labor performance. The present study was carried out to compare its sensitivity with that of a classical BALB/c 3T3 cell system. We performed the Bhas 42 cell transformation assay with inorganic arsenic compounds which are potent environmental carcinogens in human but not mutagens in bacteria or weak mutagens in mammalian cells *in vitro*. Sodium arsenite, disodium arsenate, and their metabolites, monomethylarsonic acid and dimethylarsinic acid (DMAA) were included in the study. Sodium arsenite was positive in the initiation assay and all compounds except for DMAA were positive in the promotion assay. These results were compared with reported data in a two-stage BALB/c 3T3 cell transformation assay. The sensitivity of Bhas 42 cell transformation assay was found to be similar to that of the conventional BALB/c 3T3 cell transformation assay for the detection of initiating activities of arsenic compounds. For the detection of promoting activities, its sensitivity was equivalent to that of the two-stage BALB/c 3T3 cell transformation assay where the target cells were initiated with sub-threshold dose of 3-methylcholanthrene, confirming that Bhas 42 cells behave as initiated cells in the transformation assay.

遺伝毒性学

Improvement and evaluation of High Throughput Fluctuation Ames Test using 384-well plate with *Salmonella typhimurium* TA100 and TA98

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Genes and Environment, 2009; 31(2): 47-55

Recently, it has become necessary to increase the progress of research studies into drug discovery because of the introduction of combinatorial chemistry and robotics. Therefore, genotoxicity screening assays which can be conducted with a small amount of compound, in a short time, and which can predict the results of regulatory genotoxicity tests for pharmaceuticals are required in the early stage of research. The bacterial reverse mutation test (Ames test) is a regulatory genotoxicity test and is conducted in the early stage of non-clinical safety studies. Morita established a high throughput fluctuation Ames test using 384-well plates with *Salmonella typhimurium* TA100 and TA98 (Environ. Mutagen Res. 2003, 25: 23-31), which is referred to as original FAT in the present study. Here, we report an improved high throughput fluctuation Ames test (improved FAT). The

improved FAT indicated a higher positive response than the original FAT in several mutagens. Furthermore, we evaluated the improved FAT with TA100 and TA98 using 40 National Toxicology Program (NTP) chemicals. As a result, there was 80.0% (32/40) concordance between the Ames test and the improved FAT. In conclusion, the improved FAT can predict the results of the Ames test with high concordance (especially its negative specificity). The improved FAT requires a much smaller amount of test chemicals than the Ames test (i.e., 5 mg vs 100 mg when using two tester strains) and is able to be automated. Thus, the improved FAT is considered to be useful as a screening test in the early stage of drug discovery.

[1]National Institute of Health Sciences

Practical issues on the application of the GHS classification criteria for germ cell mutagens

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Regulatory Toxicology and Pharmacology, 2009; 55(1): 52-68

The Globally Harmonized System of Classification and Labeling of Chemicals (GHS) requires classification of chemicals on germ cell mutagenicity. The Japanese government has conducted GHS classification on about 1400 chemicals in a 2-year project (J-GHS) for implementing GHS domestically. Prior to the classification work, the technical guidance for classification of germ cell mutagens was prepared. This guidance introduces the concept of heritable mutagenicity, and presents detailed criteria for germ cell mutagens, test data to be used, and a practical decision tree for classification. These practical guidance and supporting explanations are useful for non-expert Classifiers (scientists applying the classification criteria). Several issues, however, were identified during the course of J-GHS and in re-evaluating the classification results. These include: (1) the information sources when available data are limited; (2) lack of understanding GHS classification criteria or insufficient review of the information by Classifiers; (3) varying opinions of experts on data quality and weight of evidence, and; (4) decision tree approaches, e.g., inadequacy for use in overall evaluation in some cases. Ideally, classification should be performed by Classifiers with high expertise using high quality information sources. Genetic toxicologists as experts should consider data quality and reliability, and give a critical review of all available information for support of classification. A weight of evidence approach is also required to assess mutagenic potential of chemicals. Critical points for suitable classification for GHS are discussed.

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食品衛生学

Basic research on developing scallop tissue reference material for quality assurance of diarrhetic shellfish poisoning (DSP) mouse bioassay. —Stability of okadaic acid (OA)—

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Journal of Environmental Chemistry, 2010; 20(1): 1-8

The preparation of the reference material (RM) for mouse bioassay (MBA) of diarrheic shellfish poisoning (DSP) toxin was attempted. To obtain basic data on the RM, the stability of okadaic acid (OA), which causes DSP, and the method of spiking scallop tissue with OA were examined.

Microwave, ultrasonic wave, and UV, which are conventionally used in experiments or may exist in environment, did not affect on the recovery of OA. The recovery rate of OA from thermo treatment at 50-200° C was examined periodically. Results suggest that temperature has no effect on the recovery rate of OA at temperatures used during conventional analysis and transportation. However, a rapid decrease in recovery was observed during heating at more than 120° C. In addition, the half-life of OA heated in the range of 120-130° C was 1 h. OA in acetone solution that was stored in brown vials or dried at the bottom of brown vials was stable during freezing (-35° C), refrigeration, and storage at room temperature (20° C) for six months. The titer of OA tested by MBA was stable in stocked samples, but the recovery rate of OA decreased by about 10% at the HPLC level after 15 months of storage. It was clarified that the recovery rate of OA absorbed in filter paper decreased gradually but the recovery rate of OA was stable under conditions of three-week refrigeration. Samples were distributed to collaborating laboratories and their results of MBA were compared and we did not find any problems on the quality of RM or on the results of MBA quality assurance.

[1]National Institute of Health Sciences

動物実験代替法

An interlaboratory collaborative study on a cell transformation assay using Bhas 42 cells

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Alternatives to Animal Testing and Experimentation, 2009; **14(1)**: 831-848

A sensitive cell transformation assay for tumor initiators as well as promoters has been developed using a v-Ha-*ras*-transfected BALB/c 3T3 cell line, Bhas 42. In order to establish the method as a routine procedure, we have conducted a NEDO Project for the confirmation of its usefulness. Six laboratories joined in this project and examined nine chemicals, so as to be tested for a chemical by three laboratories. Judgments on carcinogenic compounds, *N*-methyl-*N*′-nitro-*N*- nitrosoguanidine and benzo[*a*]pyrene, were positive in the initiation assay and negative in the promotion assay. Although benz[*a*]anthracene is a carcinogen and pyrene is reported to be non-carcinogenic to animals, they gave positive results in both initiation and promotion assays. Anthracene, a non-carcinogen, was negative in both initiation and promotion assays. Mezerein, lithocholic acid and methapyrilene hydrochloride, known to act as tumor promoters, were judged positive in the promotion assay and negative in the initiation assay. Phorbol, a negative control for tumor-promoting phorbol esters, was shown negative in both initiation and promotion assays. In conclusion, this inter-laboratory collaborative study demonstrated that the Bhas 42 cell transformation assay is reproducible and applicable to the detection of both initiators and promoters, leaving the possibility of more improvement by the modification of the protocol and guidance for the procedure.

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医療機器

医用材料の生物学的安全性評価

小島幸一

材料の科学と工学, 2009; **46(6)**: 261-266

医用材料や医療機器を世の中に提供するためには安全性が担保されている必要がある．そのひとつとして生物学的安全性の評価も必須である．国内で必要な生物学的安全性の評価試験について解説するとともに，国際的なガイドラインとの相違を概説した．生物学的安全性評価の必要性を意識して新規素材や医療機器の開発にあたることが求められる．

薬理学

Locally applied TCP inhibits tumor growth via possible activation of macrophages

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Journal of Biomedical Materials Research Part A, 2010; **92(2)**: 542-547

The aim of this study was to investigate whether beta-tricalcium phosphate (TCP) inhibits cancer growth, because TCP, a widely used bone replacement material, is known to attract immune cells. Human colon cancer (WiDr) cells were subcutaneously injected on the backs of nude mice, and tumor growth was observed. Seven days after the injection, five animals were implanted with TCP at the tumor sites, five animals were treated by a direct application of 0.12 mg cisplatin at the sites, and four animals were not treated, as a control. Tumor size on the 43rd day of implantation was 1173 mm^3 in the TCP group and was smaller than that in the control, 1621 mm3. This inhibition was comparable to that with cisplatin. Furthermore, tumor-growing rate in the TCP group was significantly lower than that in the control group. Histopathological examination of the tumors showed migration of macrophages only in the TCP group, with TCP particles remaining at the implantation loci. There were no between-group differences in neutrophil infiltration and angiogenesis. In another series of *in vitro* experiments, a concentration-dependent increase in luminol chemiluminescence was observed in isolated human peripheral neutrophils incubated with TCP, and the chemiluminescence due to phagocytosis of opsonized zymosan in the presence of TCP occurred with a lower level of TCP than when the chemiluminescence was due to TCP alone. These results suggest that subcutaneously implanted TCP inhibits tumor growth of implanted WiDr cells, and that the activation by TCP of macrophages plays a role in that inhibition.

[1]Medical new Business Project, Corporate R&D Center, Olympus Corporation

発生神経毒性学

Observation of fetal brain in a rat valproate-induced autism model: a developmental neurotoxicity study

Makiko KUWAGATA, Tetsuo OGAWA[1,2], Seiji SHIODA[1], Tomoko NAGATA

International Journal of Developmental Neuroscience, 2009; **27(4)**: 399-405

Prenatal exposure to chemicals is well known to induce developmental abnormalities in the central nervous system of children. Developmental neurotoxicity (DNT) tests are important to identify neurotoxic agents and prevent neurodevelopmental disorders. We have investigated DNT, focusing on the fetal brain shortly after chemical exposure. To demonstrate a usefulness of a study focusing on the fetal brain in DNT tests, we assessed the fetal brain in a rat valproate-

induced autism model. Rats were treated with sodium valproate (VPA, 800 mg/kg) orally on gestational day (GD) 9 or 11 (VPA9 or VPA11), and the fetal brains were examined on GD16 using immunohistochemistry for serotonin (5-HT), tyrosine hydroxylase (TH), and TuJ1 (neuron specific class III β -tubulin). Hypoplasia of the cortical plate was induced in both VPA9 and VPA11 groups. Abnormal migration of TH-positive and 5-HT neurons, possibly due to the appearance of an abnormally running nerve tract in the pons, was observed only in the VPA11 group. In addition, when we compared the incidence of these abnormalities between pregnant rats mated in our own animal facility (in-house group), and rats purchased pregnant (supplier group), the supplier group was much more sensitive, especially to the pons abnormality. Shipping stress may affect the reproducibility of VPA-induced DNT. The present results demonstrate that examination of the GD16 fetal brain was useful for detecting and characterizing abnormal development of the brain after VPA exposure. Further discussion was made with reference to the findings in children with autism.

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Biphasic effects of neonatal allopregnanolone on striatal dopamine metabolism

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NeuroReport, 2009; **20(9)**: 860-863

Neurosteroids are known to modulate the development of the mesocorticolimbic system. We examined the effects of low (1 mg/kg) and high (10 mg/kg) doses of allopregnanolone on monoamine metabolism during the neonatal period (postnatal days 3-7) in rats. At 10 weeks of age, increases in homovanillic acid/dopamine (DA) ratios were found in the striatum in both allopregnanolone-treated groups compared with control rats. However, striatal DA levels decreased only in the low-allopregnanolone group and striatal homovanillic acid levels increased only in the high-allopregnanolone group. Allopregnanolone did not significantly affect cortical DA metabolism, or cortical or striatal serotonin metabolism. Data indicate that neonatal allopregnanolone treatment has a biphasic effect on striatal DA metabolism.

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内分泌学

Prolactin induces phosphorylation of the STAT5 in adrenal glands of Hatano rats during stress

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Life Sciences, 2009; **85(3-4)**: 172-177

Aims: To investigate the signaling of prolactin (PRL) in the adrenal gland during stress in Hatano high- (HAA) and low-avoidance (LAA) rats.

Main methods: Adrenal glands of both strains were collected at 0, 15 and 30 min after stress. The protein levels of phosphorylated STAT5 and the mRNA levels of melanocortin receptor 2 (MC2R) and PRL receptor (PRLR) were analyzed. Furthermore, the effects of bromocriptine-induced hypoprolactinemia on adrenocortical responses to stress were investigated.

Key findings: Adrenocorticotropic hormone (ACTH) concentrations in HAA were greater than LAA, while the difference in PRL concentrations were found only at 120 min after stress induction.

No strain differences were observed in corticosterone or progesterone in response to stress. The stress-induced increase in MC2R mRNA expression was higher in HAA, but there was a lowered PRLR mRNA expression. STAT5 become highly phosphorylated in response to stress in both strains, but bromocriptine led to a reduction the STAT5 phosphorylation. Exposure to bromocriptine was associated with a reduction in plasma PRL in response to stress in both strains, while the ACTH levels were not altered. However, the decrease in corticosterone and progesterone in response to stress was observed only in bromocriptine-treated LAA rats.

Significans: These data show that PRL plays an important role in the regulation of corticosterone and progesterone release in LAA but not in HAA during stress. These results suggest that PRL increase in response to stress, and it acts on the adrenal cortex and thereby plays an important physiologic role in protecting against acute stress.

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Differences in adrenocortical secretory and gene expression responses to stimulation *in vitro* by ACTH or prolactin between high- and low-avoidance Hatano rats

Sukanya JAROENPORN[1,2], Kentaro NAGAOKA[3], Ryo OHTA, Mariko SHIROTA, Gen WATANABE[1,2], Kazuyoshi TAYA[1,2]

Stress, 2009; 12(1): 22-29

Rats of the Hatano high-avoidance (HAA) and low-avoidance (LAA) strains have been genetically selected on the basis of their two-way active avoidance behavior, and have different endocrine responses to stress. The present study focused on the adrenal steroid hormone responses of the Hatano strains and identifies differences in regulation of the adrenal cortex *in vitro* of HAA and LAA rats. Although incubation with prolactin (PRL) and/or adrenocorticotrophic hormone (ACTH) resulted in a dose-dependent increase of corticosterone and progesterone release by adrenal cells from both HAA and LAA male rats, the responses were markedly increased for adrenal cells from LAA rats as compared with HAA rats. This finding suggested that adrenal glands of HAA rats are less sensitive to PRL and/or ACTH than adrenals from LAA rats. Several possible intra-adrenal regulators were investigated. The basal levels of expression of steroidogenic acute regulatory protein (StAR) and the long form of the PRL receptor (PRLR-L) mRNAs were higher in adrenals of LAA rats. ACTH treatment of adrenal cells from HAA rats resulted in statistically significant increases in melanocortin receptor 2 (MC2R) mRNA expression, while neither ACTH nor PRL altered MC2R mRNA expression in adrenal cells of LAA rats. Conversely, the increase in PRLR-L mRNA expression induced by PRL was observed only in adrenal cells from LAA rats. Treatment of adrenal cells with PRL and/or ACTH increased the expression of StAR and CYP11A1 mRNAs for both Hatano strains. However, the induction of StAR mRNA expression was higher in LAA rats, but the CYP11A1 response was lower. These findings indicate that adrenal cells of the LAA strain have higher sensitivity to secretagogues than those of the HAA strain. These results suggest that PRL may also be important in stimulating secretion of adrenal steroid hormones.

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University; [2]Laboratory of Veterinary Physiology, Faculty of Agriculture, Department of Veterinary Medicine, Tokyo University of Agriculture and Technology; [3]Laboratory of Animal Breeding and Reproduction, The University of Tokyo

学会発表等

化学・生化学

Analytical technique and quality control for food safety

Takaho WATANABE

Pittcon 2010 Symposium Japan Symposium 2010 "Analytical Technology that supports Safety and Security in Future" 2010.2.28～3.5（Orlando, USA）

同会Abstract, pp. 25-28

免疫毒性学

経口感作および経口惹起によるマウスの食物アレルギーモデル (7)

新藤智子, 香取輝美, 金澤由基子, 大沢基保, 小島幸一, 手島玲子[1]

第16回日本免疫毒性学会学術大会 2009.8.27～8.28（旭川）

同会講演要旨集, p. 71

[1]国立医薬品食品衛生研究所

食物アレルゲン性の*in vitro*評価系の開発

香取輝美, 新藤智子, 金澤由基子, 大沢基保, 小島幸一, 手島玲子[1]

第16回日本免疫毒性学会学術大会 2009.8.27～8.28（旭川）

同会講演要旨集, p. 58

[1]国立医薬品食品衛生研究所

実験動物学

BrlHan:WIST@Jcl(GALAS)由来甲状腺腫大ラットの遺伝性矮小児における，レボチロキシンナトリウム製剤投与効果

高島宏昌, 吉田由香, 瀬沼美華, 桑形麻樹子, 井上雪乃, 佐藤 旭[1], 太田 亮, 小島幸一, 青山博昭[1]

第56回日本実験動物学会総会 2009.5.14～5.16（さいたま）

同会講演要旨集, p. 184

[1]財団法人残留農薬研究所

実験動物の死後直腸温，死後硬直，死後剖検所見の推移について

堀内伸二, 藤原広和

東京実験動物研究会 2009.6.19（東京）

有効な試験にするための動物実験手技

畔上二郎

第43回日本実験動物技術者協会 2009.10.9～10.10（新潟）

同会講演要旨集, p. 70

一般毒性学

4-エチルモルホリンおよび2-(ジ-*n*-ブチルアミノ)エタノールのラットにおける腎病変の比較―アクアポリンの免疫組織学的局在

森村智美, 熊谷文明, 古谷真美, 加藤博康, 臼見憲司, 斉藤義明
第36回日本トキシコロジー学会学術年会　2009.7.6～7.8（盛岡）
Journal of Toxicological Sciences, 2009; **34(Suppl.)**: S118

SDラットにおける経口光毒性試験法の検討―5種の光毒性物質の比較―

田面喜之, 森村智美, 青木聡子, 須井　哉, 川上久美子, 豊泉友康, 関　剛幸, 太田　亮, 小島幸一
第36回日本トキシコロジー学会学術年会　2009.7.6～7.8（盛岡）
Journal of Toxicological Sciences, 2009; **34(Suppl.)**: S189

生殖・発生毒性学

ラット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, 高島宏昌, 吉田由香, 三枝克彦, 太田　亮, 小島幸一
第36回日本トキシコロジー学会学術年会　2009.7.6～7.8（盛岡）
Journal of Toxicological Sciences, 2009; **34(Suppl.)**: S124

Effects of cell recovery factor in cell differentiation culture with the embryonic stem cell test

Koichi IMAI[1], Shoji TAKEDA[1], Shinji KUSAKAWA[2], Akito TANOUE[2], Makiko KUWAGATA, Mika SENUMA, Mami FURUYA, Hiromasa TAKASHIMA
7th World Congress on Alternatives & Animal Use in the Life Sciences 2009.8.30～9.3（Rome, Italy）
Alternative to Animal Experimentation, 2009; **26, Special Issue**: 116

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Valproate-induced abnormal development neurotoxicity: fetal brain observation versus postnatal brain observation

Makiko KUWAGATA, Tetsuo OGAWA[1,2], Seiji SHIODA[1], Tomoko NAGATA
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Distribution of c-fos-like immunoreactivities in the neonatal rat brain shortly after maternal deprivation in the BrdU-induced hyperactivity model

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プロラクチンによる副腎皮質ステロイドホルモンの分泌促進作用

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Behavioral profile in ovariectomized female Hatano high- and low-avoidance rats

Maiko KAWAGUCHI[1], Ryo OHTA, Hiroko MAKIHARA[1], Gen WATANABE[2,3], Kazuyoshi TAYA[2,3], Tsutomu SHIMADA[1], Masaki ABURATA[1], Nobumasa KATO[4], Toshiyuki HIMI[1]
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Endocrine Mechanisms responsible for different ovarian follicular development during the estrous cycle between High- and Low-avoidance Hatano Rats

Yasuyuki HORII[1,2], Sukanya JAROENPORN[3], Sayaka ASAI[4], KaiMing WANG[2], Ryo OHTA, Mariko SHIROTA[5], Gen WATABABE[1,2], Kazuyoshi TAYA[1,2]

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GLP

医薬品・医療機器GLP調査・査察事例報告

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