研究業績

論文等

化学・生化学

エポプロステノール静注用「ACT」の生理食塩液中における安定性

古石誉之[1], 加藤博美, 渡辺卓穂, 上田晴久[1]

新薬と臨牀, 2014; **63**: 889-893

エポプロステノール静注用「ACT」の溶解液は患者の状態（症状，血圧，心拍数，血行動態等）により，いろいろな濃度や速度で投与される．患者は24時間持続点滴される必要があることから，在宅治療中の患者は携帯型の精密持続点滴装置が用いられる．そのため，外気温が溶解液の安定性に影響を及ぼす一因となり考慮する必要がある．一方，新生児や幼児などへの初期投与においては極めて低濃度のエポプロステノールを院内投与することも考えられる．今回，エポプロステノール静注用「ACT」溶解溶液の室温以上の温度における安定性及び低濃度，室内散乱光下における安定性を検討した．その結果，3,000～30,000 ng/mL濃度の場合，室温（～30℃）で24時間まで93.0%以上の残存率であったが，35℃あるいは40℃となるにつれて，また濃度が薄くなる程残存率の低下傾向がみられた．また，極めて低濃度の200 ng/mL濃度では室温（20.7～22.7℃），室内散乱光下で4時間，500～1,000 ng/mLでは24時間まで90%以上の残存率が確認された．

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実験動物学

第10章　実験動物・施設の管理・運用　第5節　実験動物の飼育・管理に関する管理・運営での留意点

堀内伸二

実験者／試験検査員の誤ったデータの取扱い・試験誤操作防止策, 技術情報協会, 東京（2014）, pp. 380-383

一般毒性学

「角膜実験モデル」　イントロダクション

森村智美

比較眼科研究2014; **33**: 9-11

角膜は眼球の外壁の一部であるとともに，光を屈折させて眼球内に取り込むレンズの役割も果たしており，障害を受けた場合，視力への影響は大きい．角膜最表面に位置し，常に外界と接する環境にある角膜上皮は，皮膚のような角質層はなく，生きた細胞が表層に露出していることから，障害を受けやすい．そのため，眼に適用される医薬品から，化粧品，職業曝露が懸念される化学物質に至るまで広い範囲の化学物質を対象に角膜の障害性評価が行われてきた．角膜実験モデルとしては，1944年にDraizeらによって考案されたウサギを用いた眼刺激性試験が長年主流となっており，現在でもGHSのガイドラインでは最終評価にDraize法が取り入れられている．その一方で，Draize法は，動物福祉問題の原点ともいえる実験法であり，その改良とともに，数多くの代替法が開発されてきた．代替法は大きく分けて摘出角膜組織を使用する実験モデルと，培養細胞を使用する実験モデルの2通りがある．前者には，食用目的で屠殺されたウシの角膜やニワトリの眼球を利用した試験法などがあり，後者には，ウサギやヒト由来の単層あるいは三次元培養した細胞層を用い，蛍光色素の漏出や細胞生存率を指標に評価する試

験法などがある．これら代替法は，以前はトップダウンアプローチに限られたものが多かったが，改良が進み，現在では，ボトムアップアプローチが可能となっているものもある．今回の角膜実験モデルのセッションでは，株式会社化合物安全性研究所の伊藤浩太先生に，摘出角膜試験法の代表格であるウシの摘出角膜を使用したBCOP法に病理組織学的検査を加えた評価方法について，参天製薬の阪元明日香先生には，培養細胞実験モデルにおける細胞の特徴やモデルの用途，さらにはより生体内に近い条件である三次元培養ヒト角膜上皮細胞を用いた評価法について実験データも含めてご紹介頂く予定である．さらに，再生力に乏しく，障害による細胞密度減少が深刻な角膜障害へと繋がる角膜内皮細胞に着目し，千寿製薬株式会社の坂本雄二先生に，角膜内皮研究におけるフェレットの有用性についてご講演頂き，角膜障害性を通して角膜についての知識を深める場を提供したいと考えている．

生殖・発生毒性学

Seeking genes responsible for developmental origins of health and disease from the fetal mouse liver following maternal food restriction

Tetsuo OGAWA[1], Junko SHIBATO[1], Randeep RAKWAL[1,2,3], Tomomi SAITO[1], Gaku TAMURA[1], Makiko KUWAGATA[1], Seiji SHIODA[1]

Congenital Anomalies, 2014; **54**: 195-219

Low birthweight resulting from a nonoptimal fetal environment is correlated epidemiologically to a higher risk of adult diseases, and which has also been demonstrated using animal models for maternal undernutrition. In this study, we subjected pregnant mice to 50% food restriction (FR), and profiled gene expression and promoter DNA methylation genome-wide using the fetal livers. The fact that effect of food restriction is opposite between before and after birth encouraged us to hunt for genes that are expressed oppositely to adult calorie restriction (CR) using the maternal livers. Among oppositely regulated genes, we identified *trib1* (tribbles homolog 1). Using genetically modified mice, *trib1* has been shown to have a demonstrable contribution to a risk of hypertriglyceridaemia and insulin resistance. Our data showed that the *trib1* expression and its promoter DNA methylation could be affected physiologically (by maternal nutrition), and therefore might be a strong candidate gene for developmental origins of adult diseases. Furthermore, *lepr* (leptin receptor) gene was down regulated by maternal FR, indicating its potential role in induction of obesity and diabetes. Gene expression as well as promoter DNA methylation profiling revealed that glucocorticoid receptor target genes were regulated by maternal FR. This supports previous studies that suggest an important role of fetal glucocorticoid exposure in the mechanism of developmental origins of diseases. Our transcriptomics profiling data also suggested that maternal FR impaired development of the immune system. An inventory of candidate genes responsible for developmental origins of health and disease is presented and discussed in this study.

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Ovarian dysfunction, obesity and pituitary tumors in female mice following neonatal exposure to low-dose diethylstilbestrol

Ryo OHTA, Hideo OHMUKAI, Tomoyasu TOYOIZUMI, Tomoko SHINDO, Hideki MARUMO, Hiroshi ONO

Reproductive Toxicology, 2014; **50**: 145-151

In a previous study, we found that early life exposure to low-dose diethylstilbestrol (DES) induced early onset of spontaneous abnormalities in estrus cycle and shortened survival in female Sprague-

Dawley rats. In order to confirm the repeatability of the previous study, neonates of C57BL/6J mice were orally administered DES at doses of 0.005, 0.05, 0.5 and 5 μg/kg/day, and the aging of their reproductive function was observed. As a result, delayed toxicity on ovarian function was found in females treated with 0.5 μg/kg/day of DES. Concomitantly, the females in the 0.05 μg/kg/day of DES, or greater, groups, had increased body weights and, in the 0.5 μg/kg/day of DES, or greater, groups, had developed pituitary tumors, which were causal factors in their accelerated mortality. Thus, we found that early life exposure to low-dose DES induced early onset of spontaneous abnormalities in estrus cycle not only in female rats but also in female mice.

Early to middle gestational exposure to diethylstilbestrol impairs the development of labyrinth zone in mouse placenta

Nao KAGAWA[1], Yoshiaki SAITO, Tetsuji NAGAO[1]

Congenital Anomalies, 2014; **54**: 116-119

This study was performed to clarify the involvement of impaired labyrinth zone (LZ) of the placenta in the developmental toxicity of diethylstilbestrol (DES). DES at 10 μg/kg per day was administered orally to mice on days 4 through 8 of gestation. Histological observation of the LZ and determination of blood glucose levels in dam and fetus were performed on day 13. A high frequency of embryonic death was observed in the DES group. DES induced the under development of the plexus vasculosus, extensive maternal blood space and the decreased expression of glucose transporters in the LZ, and a reduction of the glucose level in embryos. These findings suggest that impaired LZ development may be related to the embryo lethality of DES.

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細胞毒性学

High-throughput quantification of morphologically transformed foci in Bhas 42 cells (v-Ha-ras transfected Balb/c 3T3) using spectrophotometry

Kiyoshi SASAKI, Ayako SAKAI, Noriho TANAKA

In: Steinberg P. ed. "High-Throughput Screening Methods in Toxicity Testing" Hoboken, N.J.: John Wiley & Sons, (2013); pp. 317-339

Transformation assay in Bhas 42 cells: a model using initiated cells to study mechanisms of carcinogenesis and predict carcinogenic potential of chemicals

Kiyoshi SASAKI, Makoto UMEDA, Ayako SAKAI, Shojiro YAMAZAKI, Noriho TANAKA

Journal of Environmental Science and Health, Part C Environmental Carcinogenesis and Ecotoxicology Reviews, 2015; **33**: 1-35

Transformation assays using cultured cells have been applied to the study of carcinogenesis. Although various cell systems exist, few cell types such as BALB/c 3T3 subclones and Syrian hamster embryo cells have been used to study chemically-induced two-stage carcinogenesis. Bhas 42 cells were established as a clone by the transfection with v-Ha-ras gene into mouse BALB/c 3T3 A31-1-1 cells and their subsequent selection based upon their sensitivity to 12-O-tetradecanoylphorbol-13-acetate. Using Bhas 42 cells, transformed foci were induced by the treatment with non-genotoxic carcinogens, most of which act as tumor promoters. Therefore, Bhas 42 cells were considered to be a model of initiated cells. Subsequently, not only non-genotoxic

carcinogens but also genotoxic carcinogens, most of which act as tumor initiators, were found to induce transformed foci by the modification of the protocol. Furthermore, transformation of Bhas 42 cells was induced by the transfection with genes of oncogenic potential. We interpret this high sensitivity of Bhas 42 cells to various kinds of carcinogenic stimuli to be related to the multistage model of carcinogenesis, as the transfection of v-Ha-ras gene further advances the parental BALB/c 3T3 A31-1-1 cells toward higher transforming potential. Thus, we propose that Bhas 42 cells are a novel and sensitive cell line for the analysis of carcinogenesis and can be used for the detection of not only carcinogenic substances but also gene alterations related to oncogenesis. This review will address characteristics of Bhas 42 cells, the transformation assay protocol, validation studies and the various chemicals tested in this assay.

医療機器

第6章　医薬品の品質(CMC)に関する規制で特に留意すべきポイント　第3節　医療機器

小島幸一

医薬品/医療機器の承認申請書の上手な書き方・まとめ方　～審査に不可欠なデータ・情報の取得の仕方～, 技術情報協会, 東京(2014), pp. 259-270

医療機器の安全性に関しては，生物学的安全性，電気的安全性，機械的安全性などが求められる．なかでも生物学的安全性については，培養細胞や動物などを用いて実施した試験のデータを基にして評価されるために，理解するのに困難を感ずることも少なくない．加えて，医療機器においても海外への展開あるいは海外からの導入などが盛んであり，生物学的安全性にかかわる国際的な相互のデータの活用がどのような状況にあるのかも気にかかることである．本節では，生物学的安全性試験の３極間の主要な相違点を示すことによって，海外データの国内での利用ならびに国内データの海外での利用に当たっての留意点などを述べる．

医用材料，医療機器の生物学的安全性評価

小島幸一

日本材料科学会誌「材料の科学と工学」2014; **51**: 186-189

医療機器に用いる医用材料は，材料に要求される機能とともに生体に対する適合性の内容も異なってくる．一方，生物学的安全性の面から見ると，適用部位，適用期間などによって評価の項目が異なり，基本的に必要な評価項目はガイドラインとして提示されている．医用材料や医療機器を医療の場に提供するためには目的とする機能はもちろん，安全性の担保も重要な因子である．必要な生物学的安全性の評価試験とともに，その根拠となる規制等の概要を解説した．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ている．

Trehalose solution protects mesothelium and reduces bowel adhesions

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Journal of Surgical Research, 2014; **191**: 224-230.

BACKGROUND: Preventing interbowel adhesions still remains a challenge. Peritoneal mesothelial damage can induce postoperative adhesions. Our study evaluated the effects of 3% trehalose solution on mesothelial protection and adhesion prevention. Also, we compared this novel solution with Seprafilm regarding efficacy.

METHODS: Mesothelial damage was induced on the cultured human mesothelial cell (Met-5A)

and rabbit cecum-serosal surface by air-drying for 60 min, and trehalose solution was applied. Cell integrity was tested by measuring lactate dehydrogenase, and serosal-morphologic changes were analyzed using scanning electron microscopy. Intra-abdominal adhesions were induced in rabbits by the combination of abrasion and air-drying procedures. Animals were divided into four groups: control, 3% trehalose solution, Seprafilm, and 3% trehalose solution with Seprafilm. Adhesions were evaluated blindly 7 d later.

RESULTS: Lactate dehydrogenase release from the Met-5A cells was reduced dose-dependently by trehalose ($P<0.05$). Morphologic studies clearly showed that mesothelial cells on the serosal surface were kept intact by 3% trehalose solution. In a rabbit adhesion model, 3% trehalose solution reduced adhesions between bowel and bowel or bowel and surrounding structures ($P<0.01$ versus control and Seprafilm). Seprafilm reduced adhesions between abdominal wall and underlying viscera ($P<0.01$ versus control and 3% trehalose solution). Three-percent trehalose solution with Seprafilm showed additive effects of adhesion prevention, reducing adhesion formation at the previously mentioned sites.

CONCLUSIONS: Three-percent trehalose solution protects mesothelial cells and leads to reduced adhesions between bowel and bowel or bowel and surrounding structures. This effect seems to be resulted from the characteristics of the solution covering most areas that potentially develop adhesions.

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In vitro and *in vivo* Evaluation of Hemocompatibility of Silk Fibroin Based Artificial Vascular Grafts

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International Journal of Chemistry, 2014; **6**: 1-14.

Artificial vascular grafts with low thrombogenicity are generally required to avoid blood platelet adhesion and to minimize intimal hyperplasia, thus retaining vascular patency. In this study, we aimed to determine the acute and subacute hemocompatibility of silk fibroin (SF) grafts by *in vitro* and *in vivo* evaluation. Blood contact reaction with SF grafts was examined by thrombin-anti-thrombin III complex (TAT) formation, platelet activation level by β-thromboglobulin (β-TG), complement system response (C3a and SC5b-9), platelet and fibrin deposition and compared with commercially available polyethylene terephthalate (PET) artificial grafts *in vitro*. The biocompatibility and coagulation-inducing effect of coating materials were evaluated by *in vivo* implantation in rats. Two weeks after implantation, SF grafts showed low subacute coagulation. All blood parameters evaluated for animals implanted with SF-coated grafts showed almost the same values as those for sham-operated animals. Our results support the suggestion that SF will be a suitable material for vascular regeneration in future.

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Development and performance evaluation of a positive reference material for hemolysis testing

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Journal of Biomedical Materials Research Part B: Applied Biomaterials, 2014; **102**: 1809-1816

This study deals with the development and performance evaluation of a positive reference

material for hemolysis testing, which is used for evaluating the biological safety of medical devices. Genapol X-080, a nonionic detergent, was selected as a candidate hemolytic substance in a survey of 23 chemical compounds; it showed significant hemolytic activity against rabbit defibrinated blood at concentrations more than 20 μg/mL. A polyvinyl chloride (PVC) sheet spiked with 0.6% (w/w) of the compound exhibited weak hemolytic activity in direct contact and/or extract-based assays after 4 h incubation at 37℃. A PVC sheet containing 5.8% (w/w) Genapol X-080 induced complete hemolysis in both assays. The amount of Genapol X-080 eluted from each PVC sheet during hemolysis testing using the direct contact method increased time-dependently and reached 25.6 (former sheet) or 1154 (later sheet) μg/mL after 4 h incubation, which was similar to or much higher than the critical micelle concentration, respectively. Similar elution behavior was observed using the extract-based method, and the Genapol X-080 content in test solutions prepared by autoclave extraction of both sheets was 22.5 and 358 μg/mL, respectively, indicating a clear relationship between the degree of hemolytic activity and the eluted amount of Genapol X-080. Thus, a PVC sheet spiked with a compound exhibiting different hemolytic activity depending on its concentration may be useful as a positive reference material to validate the hemolysis tests.

[1]Division of Medical Devices, National Institute of Health Sciences; [2]Division of Environmental Chemistry, National Institute of Health Sciences; [3]Kawasumi Laboratories, Inc., Corporate Research and Development Division; [4]R&D Headquarters, Evaluation Center, TERUMO Corporation; [5]Office of Standards and Guidelines Development, Pharmaceuticals and Medical Devices Agency

動物実験代替法

BG1LucER TA (LUMI-CELL ER) 法：*in vitro* ヒトエストロゲン受容体活性化物質試験法の評価

小野　宏，丸野内棣[1]，井口泰泉[2]，中澤憲一[3]

AATEX-JaCVAM, 2014; **3**: 97-114

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発達神経毒性学

Prenatal sodium arsenite affects early development of serotonergic neurons in the fetal rat brain

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International Journal of Developmental Neuroscience, 2014; **38**: 204-212

Prenatal arsenite exposure has been associated with developmental disorders in children, including reduced IQ and language abnormalities. Animal experiments have also shown that exposure to arsenite during development induced developmental neurotoxicity after birth. However, the evidence is not enough, and the mechanism is poorly understood, especially on the exposure during early brain development. This study assessed effects of sodium (meta) arsenite shortly after exposure on early developing fetal rat brains. Pregnant rats were administered 50 mg/L arsenite in their drinking water or 20 mg/kg arsenite orally using a gastric tube, on gestational days (GD) 9-15. Fetal brains were examined on GD16. Pregnant rats administered 20 mg/kg arsenite showed reductions in maternal body weight gain and food consumption during treatment, but not with 50 mg/L arsenite. Arsenite did not affect fetal development, as determined by body weight, mortality and brain size. Arsenite also did not induce excessive cell death or affect neural cell division in any region of the fetal neuroepithelium. Tyrosine hydroxylase immunohistochemistry revealed no difference in the

distribution of catecholaminergic neurons between fetuses of arsenite treated and control rats. However, reductions in the number of serotonin positive cells in the fetal median and dorsal raphe nuclei were observed following maternal treatment with 20 mg/kg arsenite. Image analysis showed that the serotonin positive areas decreased in all fetal mid- and hind-brain areas without altering distribution patterns. Maternal stress induced by arsenite toxicity did not alter fetal development. These results suggest that arsenite-induced neurodevelopmental toxicity involves defects in the early development of the serotonin nervous system.

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遺伝毒性学

Genotoxic potential and *in vitro* tumor-promoting potential of 2-dodecylcyclobutanone and 2-tetradecylcyclobutanone, which are radiolytic products of fatty acids

Kohji YAMAKAGE, Hajime SUI, Ryo OHTA, Tomoyasu TOYOIZUMI, Kumiko KAWAKAMI, Hirotaka MATSUMOTO, Toshitaka TAKAHASHI, Kiyoshi SASAKI, Mayu IKEZUMI, Saki NEGISHI, Keisuke IZUMI[1], Setsuko TODORIKI[2], Kondo TAKASHI[3], Masakazu FURUTA[4]

Mutation Research, 2014; **770**: 95-104

The DNA-damaging and tumour-promoting effects of two 2-alkylcyclobutanones (2-ACBs), which are found in irradiated fat-containing foods, were investigated by use of the comet assay and in an azoxymethane (AOM)-induced colon-carcinogenesis study in rats, respectively. We conducted genotoxicity tests of 2-dodecylcyclobutanone (2-dDCB) and 2-tetradecylcyclobutanone (2-tDCB) according to the test guidelines for chemicals or drugs. In addition, a cell-transformation assay with Bhas 42 cells was performed to investigate their promoting potential *in vitro*. The *Salmonella typhimurium* mutagenicity assay (Ames test), conducted with five tester strains, revealed that neither 2-dDCB nor 2-tDCB possessed mutagenic activity. Moreover, both in the *in vitro* chromosomal aberration test on CHL/IU cells and the *in vivo* bone-marrow micronucleus test where mice were given 2-dDCB and 2-tDCB (orally, up to 2000 mg/kg bw/day), we did not detect any clastogenic effects. Furthermore, DNA strand-breaks were not detected in the *in vitro* comet assay with CHL/IU cells, and DNA adducts derived from 2-dDCB and 2-tDCB were not detected in the colon tissues of the mice used for the micronucleus tests, in rats from a repeated dose 90-day oral toxicity test (0.03% 2-tDCB in the diet), or in rats from the AOM-induced carcinogenesis study (0.025% 2-tDCB in the diet). An *in vitro* tumour-promotion assay with Bhas 42 cells revealed that the number of transformed foci increased significantly following treatment of cells in the stationary phase with 2-dDCB or 2-tDCB for 10 days. Our results indicate that neither 2-dDCB nor 2-tDCB were genotoxic chemicals. However, they exhibited promoting activity, at least *in vitro*, when Bhas 42 cells were continuously exposed to these chemicals at toxic doses.

[1]Department of Molecular and Environmental Pathology, Institute of Health Biosciences, the University of Tokushima Graduate School; [2]Food Safety Division, National Food Research Institute; [3]Department of Radiological Sciences, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama; [4]Laboratory of Quantum-beam Chemistry and Biology, Radiation Research Center, Osaka Prefecture University

学会発表等

免疫毒性学

重金属を中心とする環境物質の免疫毒性の特性と評価
大沢基保
第21回日本免疫毒性学会学術年会2014.9.11～9.12(徳島)
同会講演要旨集, pp. 31-32

刺激性物質とLLNA－擬陽性識別の検討
高岡　裕, 森村智美, 関　剛幸, 青木聡子, 西垣嘉人, 太田　亮
第41回日本毒性学会学術年会2014.7.2～7.4(神戸)
同会講演要旨集, p. S305

医療機器のマウス局所リンパ節試験(LLNA)のための媒体の検討
森村智美, 高岡　裕, 関　剛幸, 青木聡子, 西垣嘉人, 太田　亮
第41回日本毒性学会学術年会2014.7.2～7.4(神戸)
同会講演要旨集, p. S305

毒性病理学

ガイドライン試験を補完する新たな動物試験法：胎児あるいは新生児脳を用いた試験
桑形麻樹子
第41回日本毒性学会学術年会2014.7.2～7.4(神戸)
同会講演要旨集, p. S85

皮膚バリア破綻とナノ銀粒子皮膚透過性の検討
熊谷文明, 関　剛幸, 松本亜紀, 古谷真美, 福永裕基, 等々力舞, 千坂亜希子, 臼見憲司, 野口　聡, 丸茂秀樹, 斉藤義明, 吉岡靖雄[1], 堤　康央[1], 桑形麻樹子
第31回日本毒性病理学会総会及び学術集会 2015.1.29～1.30(東京)
同会講演要旨集, p. 75
[1]大阪大学大学院薬学研究科毒性学分野

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