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文字

ラット筋芽細胞株（L6）とヒト横紋筋肉腫細胞株（RD）におけるペクテノトキシン-2と他の酸化ペクテノトキシンの細胞毒性の比較

Vol.2、No.1、p.49-54

松島亮二、菊辻沙織、渡部龍一、内田肇、安本武、永井泰宇、金庭正樹、鈴木敏幸
リリース：2015年2月3日

概要 全文PDF [1M]

親油性毒素ペクテノトキシン-2（PTX2）は、ホタテガイ*Patinopecten yessoensis*において、酸化的にペクテノトキシン-1（PTX1）、ペクテノトキシン-3（PTX3）、およびペクテノトキシン-6（PTX6）に代謝されます。この特定の代謝は、PTX6が最も優勢な親油性毒素である日本のホタテガイでのみ観察されています。ラット細胞株（L6）とヒト細胞株（RD）におけるPTX2とその代謝物PTX1,3,6の細胞毒性を調査しました。RDは、ＰＴＸへの曝露時にL6よりも約3倍高い感度を示しました。ＰＴＸの細胞毒性は、酸化の程度とともに、ＰＴＸ２＞ ＰＴＸ１＞ ＰＴＸ３＞ ＰＴＸ６の順序で減少した。計算された最大阻害濃度の半分（IC_{50}）L6およびRD細胞株で得られたPTX2の値はそれぞれ60および23 ng / mLでしたが、両方の細胞株でPTX6で得られた値は2,000 ng / mLを超えていました。これらの結果は、PTX6が極めて低い細胞毒性を持っているか、非毒性であり、中PTX2の酸化的代謝ということを証明しているP.のyessoensisは解毒プロセスです。

ページトップ

原著

肝毒性の評価のためのヒト肝細胞スフェロイドの有用性

Vol.2、No.1、p.41-48

荻原拓夫、岩居由希子、井上順子、片木淳、松本典仁、本井誠荒川博、長井大一
リリース：2015年1月21日

概要 全文PDF [489K]

薬物誘発性肝毒性は、候補臨床薬の開発を中止する一般的な理由です。本研究では、モデル薬のパネルを使用して、肝毒性の予測のための三次元培養ヒト肝細胞（スフェロイド）の有用性を調査しました：アセトアミノフェン、ベンズブロマロン、クロルプロマジン、シクロスポリンA、ジクロフェナク、フィアルリジン、フルタミド、イミプラミン、イソニアジド、チクロピジンとトログリタゾン。培養スフェロイドは、2日から7日でアルブミン分泌の有意な増加を示しました。分泌は14日で減少し始めましたが、14日から21日まで続きました。スフェロイドの形態は21日間よく維持されました。肝毒性薬物へのスフェロイドの長期曝露は、アルブミン分泌の濃度依存性抑制およびアスパラギン酸アミノトランスフェラーゼ（AST）漏出の上昇をもたらしました。$_{50}$）アルブミン分泌の減少の値は、7日から14日に変化しましたが、ジクロフェナクを除いて、14日と21日で同様の値が得られました。IC_{50}値とAST漏出の1.2倍の上昇（F1.2）を誘発する薬物濃度の値は14日と21日で類似していたため、14日の潜伏期間で十分であると考えられました。すべての薬物の$_{IC50}$値とF1.2値の間の決定係数（R^2）は0.335でした。シクロスポリンAとfialuridineを除外した場合には、Rの値^{2は} 0.887となりました。結果は、提案されたヒト肝細胞スフェロイドアッセイが、臨床薬剤候補の初期開発段階における肝毒性の評価に役立つはずであることを示しています。

ページトップ

文字

Effects of prenatal exposure to low doses of diethylstilbestrol on motor activity in newborn mice

Vol.2, No.1, p.37-39

Kaho Ozaki , Nao Kagawa , Munekazu Komada , Tetsuji Nagao
Released: January 16, 2015

Abstract Full Text PDF[200K]

We developed a newborn mouse behavioral testing method to evaluate the risk of neurotoxicity of environmental toxicants, based on determining a newborn's motor activity by applying the tare function of an analytical balance. Motor activities of newborn ICR mice exposed prenatally to diethylstilbestrol (DES) at 0.005-0.5 μg/kg/day on days 5 through 18 of gestation were evaluated on postnatal day 1. The activities of male newborns in the 0.05 μg/kg/day group were significantly increased compared to those of the controls, and the increasing tendencies were observed in both sexes of the highest group. The findings indicate that prenatal exposure to low doses of DES causes hyperactivity in newborn mice.

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Original Article

Impact of different blood sampling techniques on plasma biomarkers for skeletal myopathy in conscious rats

Vol.2, No.1, p.25-36

Kyoko Miwa , Satoshi Tamai , Yasuhiro Kinpara , Satomi Komatsu , Mayumi Goto , Takuma Iguchi , Takami Suzuki , Wataru Takasaki , Kazuhiko Mori
Released: January 16, 2015

Abstract Full Text PDF[955K]

To characterize variability of various musculoskeletal biomarkers by different blood sampling techniques in conscious rats, plasma asparate aminotransferase (AST), creatine kinase (CK) and its isoenzymes, fatty acid binding protein 3 (FABP3), myosin light chain 3 (Myl3) and microRNA (miR-133a) obtained by jugular venipuncture (C-JV) or tail venipuncture (C-TV) were compared with those obtained by jugular venipuncture (A-JV) in isoflurane-anesthetized rats. Plasma CK, FABP3 and Myl3, especially when collected by C-TV, were higher with larger variability than when collected by A-JV, whereas miR-133a displayed large variability in all techniques. Interestingly, higher CK obtained by C-JV or C-TV was largely attributable to higher CK-MM or CK-BB, respectively. Handling and restraint stress were identified as possible factors contributing to larger variability for CK, FABP3 and Myl3. A close correlation between CK and FABP3 was demonstrated both in the C-JV and C-TV techniques. Next, we evaluated the impact of C-JV and C-TV techniques for detecting skeletal myopathy in 2,3,5,6-tetramethyl-p-phenylenediamine-treated rats. In this model, CK and CK-MM obtained by C-TV were significantly increased, but those obtained by C-JV were not modified. In contrast, AST, FABP3, Myl3 and miR-133a obtained by both techniques were drastically elevated to a similar extent. The results suggest that, in conscious rats, the tail venipuncture technique may be more appropriate to detect skeletal myopathy despite the higher variability with this technique than with the jugular venipuncture technique. Furthermore, FABP3, Myl3 and miR-133a may serve as more sensitive biomarkers with large signal-to-noise ratios regardless of the blood sampling technique in conscious rats.

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Letter

Silica nanoparticle-induced toxicity in mouse lung and liver imaged by electron microscopy

Vol.2, No.1, p.19-23

Katsuhiro Isoda , Masuo Kondoh , Yasuo Yoshioka , Yasuo Tsutsumi , Takayoshi Imazawa , Tetsuji Nishimura , Isao Ishida , Kiyohito Yagi
Released: January 16, 2015

Abstract Full Text PDF[3M]

Nanomaterials have been proposed as novel substrates for medical and commercial applications. However, such materials also may have novel toxicities, thus posing environmental and health concerns. We previously reported hepatic injury in mice following the intravenous administration of unmodified silica particles with diameters of 70 nm (SP70); this toxicity was not observed following administration by the same route of micro-size particles with diameters of 300 nm (SP300) or 1,000 nm (SP1000). In the present study, we used electron microscopy to investigate the dynamics of silica nanoparticles administered in mice. SP70 was observed in hepatocytes and in lung epithelial cells. Inclusion within hepatocytes was associated with accumulation of SP70 in the liver sinusoidal endothelial cells and passage through the space of Disse. In contrast, SP300 and SP1000 were not observed within the hepatocytes. To our knowledge, our report represents the first demonstration that silica nanoparticles accumulate in hepatocytes, liver sinusoidal endothelial cells, Kupffer cells, and lung tissue; accumulation of SP70 in liver sinusoidal endothelial cells correlated with the induction of liver injury.

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Original Article

Effects of sub-chronic exposure to deltamethrin on shuttle-box avoidance and contents of amino acid neurotransmitters in hippocampus of mice

Vol.2, No.1, p.9-17

Cao Pei , Ma Ning , Gao Peng , Feng Yong-quan , Wang Xiao-dan , Xu Hai-bin
Released: January 13, 2015

Abstract Full Text PDF[1M]

The purpose of this study was to evaluate the effects of sub-chronic exposure to deltamethrin in lower doses on the acquisition of a two-way avoidance task and the levels of amino acid neurotransmitters in hippocampus of mice measured using shuttle-box and LC-MS/MS system. Deltamethrin was given to mice respectively at doses of 0.46, 0.92, 1.80 mg/kg BW daily for 60 days by gavage. Deltamethrin was found to decrease the number of avoidance responses, increase response latency, and increase glutamate levels in the 0.92 and 1.80 mg/kg BW-dose group. As revealed by electron microscopy, in 0.92 and 1.8 mg/kg-dose group mice, morphology of cells were changed and degeneration and necrosis morphological characteristics obviously were appeared. Collectively, results from this study suggest that deltamethrin may have cumulative effects in mice following repeated dosing of deltamethrin using moderately effective doses, beside Na^+ and Ca^{2+} channels as well as Na^+ and Ca^{2+}-dependent glutamate release, may be involved with neurotoxic action of deltamethrin.

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Original Article

Effect of nanoparticles injected into larvae on spermatogenesis in the pupal testis of the sweet potato hornworm, *Agrius convolvuli* (L.)

Vol.2, No.1, p.1-8

Miyoko Kubo-Irie , Masami Shimoda , Azumi Sato , Kyhota Shida , Terumi Yamaguchi , Hideo Mohri , Ken Takeda , Masaru Irie
Released: January 13, 2015

Abstract Full Text PDF[3M]

Lepidopteran species fly freely in the environment and their larvae feed on the leaves of host plants which may be exposed to nanomaterials. As an ecological model of nanoparticle exposure, 5th instar larvae of the sweet potato hornworm (*Agrius convolvuli*) were subcutaneously injected with suspensions of 10 μL (100 μg/mL) titanium dioxide nanoparticles (TiO_2-NPs), 10 μL (100 μg/mL) zinc oxide nanoparticles (ZnO-NPs) or saline (control) and the effects on spermatogenesis were examined in the pupal testis. During the larval wandering stage, larval tissues (except the testis) underwent extremely rapid histolytic changes. Pupation

and emergence were not affected by the injection. On pupal day 4, there was a significant decrease in testis weight and the number of sperm bundles in the ZnO-NPs group. Electron microscopic observation revealed that cyst cells surrounding the spermatogenic cells took on small agglomerates of TiO_2-食作用によるNPまたはZnO-NP。ナノ粒子を注入したグループで精子形成が進むにつれて、精母細胞の核にさまざまなサイズの液胞が見つかり、精子細胞の核クロマチンは凝縮せず、精子束の核にいくつかの液胞が見つかりました。これの考えられるメカニズムは、異常な液胞がクロマチン凝縮を妨害し、精子束の減少をもたらすことです。製造されたTiOの毒性$_2$ -NPs及びZnO-NPは昆虫精子形成への損害を示しました。

ページトップ

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