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文字

SK-N-SHヒト神経芽細胞腫細胞における柑橘類ポリメトキシフラボノイドであるノビレチンの小胞体ストレス誘導能の推定 Vol.1、No.4、p.169-172

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概要 全文PDF [363K]

柑橘系のポリメトキシフラボノイド化合物であるノビレチンは、認知症や糖尿病などのさまざまな病気の薬や機能性食品の開発に役立つと考えられています。したがって、その毒性効果を理解することが重要です。我々は以前、100μMの用量でのノビレチン処理がDDIT3およびTRIB3遺伝子およびタンパク質の発現を誘導したことを報告しました。これらは一般にSK-などの3つの細胞株で小胞体（ER）ストレスによって引き起こされるアポトーシスに寄与することがよく知られています。 N-SHヒト神経芽細胞腫細胞。したがって、それらの発現の増加は、ノビレチンが小胞体ストレスを誘発することによって毒性効果を発揮する可能性があるという懸念を引き起こします。本研究では、SK-N-SH細胞を100μMのノビレチンまたは1μg/ mLのツニカマイシン（小胞体ストレスの強力な誘導因子）で3、6、12、および24時間処理しました。これらのタンパク質の最大発現は後で現れ、ツニカマイシン処理細胞よりもノビレチン処理細胞の方がはるかに弱かった。小胞体ストレスに応答して増加するシャペロンの1つであるBiPタンパク質の発現レベルは、ノビレチン処理細胞では変化しませんでしたが、ツニカマイシン処理の開始後12時間および24時間で強く誘導されました。さらに、カスパーゼ-3およびポリ（ADP-リボース）ポリメラーゼの切断は、ツニカマイシン治療の開始後24時間で発生しましたが、ノビレチン治療中のどの時点でも切断は発生しませんでした。したがって、ノビレチンはDDIT3およびTRIB3の発現を誘導する能力を持っていますが、少なくとも100μMまでの用量でのこれらの増加したレベルは、アポトーシスを引き起こす小胞体ストレスを引き起こすのに十分ではありません。

ページトップ

毒物学レポート

HK-2細胞のカドミウム毒性における*GPRC5B*の関与 Vol.1、No.4、p.165-167

金庸、徳本真希、藤原康之、モー・ヨル、佐藤允彦
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概要 全文PDF [754K]

Cadmium (Cd) is a nephrotoxic heavy metal. Several signal transduction pathways have been reported to be associated with Cd toxicity. GPRC5B is a member of the family of G-protein-coupled receptors, which recognize various ligands and can transmit signals from the cell surface into the cell interior. We examined the involvement of GPRC5B in Cd toxicity in HK-2 human proximal tubular cells. Herein, we found that Cd significantly reduced *GPRC5B* gene expression in HK-2 cells. Moreover, knockdown of *GPRC5B* by siRNA transfection strengthened Cd toxicity in HK-2 cells. Our findings suggest that Cd partially conferred its toxicity by suppressing *GPRC5B* gene expression in HK-2 cells.

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Toxicomics Report

CDC23 knockdown reinforces methylmercury sensitivity in HEK293 cells Vol.1, No.4, p.161-164

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Released: December 24, 2014

Abstract Full Text PDF[1M]

The ubiquitin-proteasome system is believed to play an important role in the determination of cell sensitivity to methylmercury. The ubiquitin ligase enzyme is involved in the recognition of substrate proteins that are degraded by the ubiquitin-proteasome system. In this study, the ubiquitin ligase species affecting methylmercury sensitivity was investigated by the gene interference method. We found that the inhibition of expression of the gene for Cell division cycle 23 (CDC23), a constitutional component of the ubiquitin ligase anaphase promoting complex/cyclosome, sensitized HEK 293 cells to methylmercury.

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Original Article

Safety evaluation of mutagenecity, acute and subacute toxicity study of *Chlorella vulgaris* CK-22 in rats Vol.1, No.4, p.151-159

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Released: December 22, 2014

Abstract Full Text PDF[333K]

The aim of this study was to evaluate the safety of *Chlorella vulgaris* CK-22 as a food supplement. We examined mutagenicity, acute toxicity and subacute toxicity using Wistar rats administered *Chlorella* powder (CP). In the mutagenesis test, CP exhibited no mutagenecity in the *in vitro* assay. In the acute toxicity test, CP was administered orally at 0 mg/kg, 1,000 mg/kg, 2,000 mg/kg and 5,000 mg/kg body weight to Wistar rats (five animals/sex/group). No significance changes were observed test article-related during the 14-day observation period. The LD_{50} of CP was estimated to be more than 5,000 mg/kg body weight in rats. In the subacute toxicity test, CP was administered at 0%, 2.5%, 5% and 10% in pelleted rodent diet to Wistar rats (ten animals/sex/groups). No mortality or treatment-related clinical signs were observed in any of the groups during the 28-day observation period. In both sexes, renal histopathology was conducted in the control and 10% groups, because absolute and relative renal weights increased in the 10% groups compared to the control groups. Based on the histopathology of the kidneys, the no-observed-adverse-effect level (NOAEL) is greater 8.57 g/kg body weight/day for males and 8.62 g/kg body weight/day for females.

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Original Article

Apoptotic activities of the extract from *Moringa oleifera* leaves on human HCT116 colon cancer cells Vol.1, No.4, p.143-149

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Released: December 16, 2014

Abstract Full Text PDF[664K]

Moringa oleifera Lamk. (*M. oleifera*) is an edible plant and used for traditional medicine formulation. Some bioactive phytochemicals found in *M. oleifera* leaves thus far were identified as quercetin, chlorogenic acid, astragalin, and kaempferol. The flavonoid kaempferol was reported to induce apoptosis in human HCT116 colon cancer cells. Here, we investigated the anti-proliferative activity present in the methanol extract from *M. oleifera* leaves toward human HCT116 colon cancer cells. Fractionation of the methanol extract from *M. oleifera* leaves by gel filtration chromatography on Sephadex LH-20 enabled us to find anti-proliferative and apoptosis-inducing activities. Treatment of HCT116 cells with each pooled fraction (pf1, pf2, or pf3)

inhibited the cell proliferation in a dose-dependent manner, and the inhibitory activities contained in pf2 and pf3 were more potent than that in pf1. Compared with kaempferol, pf1, pf2, and pf3 were found to exhibit strong anti-proliferative effects on HCT116 cells. Futhermore, treatment with pf1 induced much larger numbers of cleaved caspase-3-positive cells than that with pf2 or pf3. The apoptosis-inducing activity found in each pooled fraction was higher than that of kaempferol. Cells treated with pf2 displayed the typical characteristics of apoptosis, such as membrane blebbing, nuclear condensation and apoptotic bodies, whereas cells treated with pf1 showed early apoptotic morphologies. In contrast, pf3 barely induced apoptosis despite its strong inhibition of cell proliferation. Taken together, these results suggest that, in addition to kaempferol, *M. oleifera* leaves may contain new substances having anti-proliferative and apotosis-inducing activities on HCT116 cells.

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Letter

Effects of a repeated low dose of LiCl injection under conditioned taste/flavor aversion using xylene — Vol.1, No.4, p.135-142

Rieko Hojo , Mitsutoshi Takaya , Yukie Yanagiba , Akinori Yasuda , Masao Tsuchiya , Yasutaka Ogawa
Released: December 08, 2014

Abstract Full Text PDF[276K]

We examined whether repeated injections with low-doses lithium chloride (LiCl) as unconditioned stimulus (US) established conditioning as applied conditioned taste aversion (CTA) experiment, using xylene solution as a conditioned stimulus (CS). In the conditioning procedure, water-deprived male rats were exposed to xylene solution for 30 min, followed by LiCl or saline injection. As a two-bottle test, xylene solution and usual drink water were simultaneously provided to rats on the next day of the conditioning and measured each consumption volume. Conditioning and two-bottle test were repeated eight times respectively by turns. Groups of no treatment and sham injection after xylene ingestion were added to verify the effects of external contexts on establishment of CTA. Results indicate that the CTA was gradually established when the US was repeatedly presented even if the US was very low concentration, and the organic solvent functioned as CS even if it was not so desirable for animals. External contexts, such as handling and the 'pain' induced by injection, did not affect the establishment of the CTA in the present study. Although xylene was used as solution in the present study and defined as flavor stimulus, gas should be used to examine the effects of odor stimulus.

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Toxicomics Report

Effects of cadmium on the gene expression of *SLC39A1* coding for ZIP1 protein — Vol.1, No.4, p.131-133

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Abstract Full Text PDF[413K]

Cadmium (Cd) is a toxic heavy metal, particularly in the kidney. Zinc transporters have been reported to be responsible for the absorption of Cd in the kidney. Interestingly, we previously found in a DNA microarray that exposure to Cd suppressed the expression of the gene coding for the zinc transporter ZIP1 (*SLC39A1*) in HK-2 human kidney proximal tubular cells. In this study, we validated by realtime RT-PCR that *SLC39A1* gene expression was indeed decreased upon treatment with 40 μM Cd. We also demonstrated that knockdown of *SLC39A1* by siRNA transfection conferred resistance to Cd in HK-2 cells. Together, this suggests that gene suppression of *SLC39A1* by Cd is involved in the defense mechanism against the Cd toxicity in HK-2 cells.

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Original Article

The paradoxical effect of 1,4-naphthoquinone on the process of cell death induced by hydrogen peroxide in rat thymocytes

Vol.1, No.4, p.123-129

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Abstract Full Text PDF[937K]

1,4-Naphthoquinone (NAPH) is found in diesel exhaust particles and it is an active metabolite of naphthalene, a fumigant insecticide. This compound is known to cause oxidative stress. Therefore, it is plausible to suggest that NAPH increases cell vulnerability to oxidative stress in an additive or synergistic manner. We tested this possibility using rat thymocytes with flow-cytometric techniques and appropriate fluorescent probes. NAPH attenuated the increase in cell lethality induced by hydrogen peroxide (H_2O_2). The combination of NAPH and H_2O_2 promoted the transition from normal cells to apoptotic living cells, but attenuated further transition to cell death. Thus, the process of cell death induced by H_2O_2 was not completed in the presence of NAPH. However, NAPH did not attenuate certain lethal cellular events such as decrease in the cellular content of non-protein thiols and increases in intracellular Ca^{2+} and Zn^{2+} levels, induced by H_2O_2. The inhibitory effect of NAPH on the increase in cell lethality induced by H_2O_2 was also observed when caspase activity was suppressed. In the present study, the mechanism underlying the NAPH-induced attenuation of cell death in cells affected by H_2O_2-generated oxidative stress was, however, not fully elucidated. Since both H_2O_2 and NAPH elevated intracellular Ca^{2+} and Zn^{2+} levels, and since Zn^{2+} is known to partly attenuate Ca^{2+}-dependent cell death, the intracellular interaction between Ca^{2+} and Zn^{2+} may complicate the process of cell death induced by oxidative stress.

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Original Article

Diallyl disulfide administration increases the number of B-lymphocytes in the rat spleen

Vol.1, No.4, p.115-121

Yoko Hashizume , Ken Shirato , Kaoru Tachiyashiki , Kazuhiko Imaizumi
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Abstract Full Text PDF[395K]

Diallyl disulfide (DADS), the major sulfur compound in garlic, reduces the number of circulating T-lymphocytes, B-lymphocytes, and monocytes via activation of the hypothalamus-pituitaryadrenal axis. However, the translocation of those cells that migrate in response to DADS administration is still unclear. Therefore, in this study, we examined the effects of DADS administration on a number of lymphocyte subsets and monocyte-derived cells including macrophages (monocytes/macrophages) in spleen, the largest secondary lymphoid organ. Ten-wk-old male Sprague-Dawley rats were orally administered with DADS (dose = 20 mg/kg body weight) or equivalent volume of vehicle. The spleen was harvested 4 hr after administration, and then the splenic cells were isolated and the total number of cells was counted. T-lymphocytes, B-lymphocytes, natural killer (NK) cells, and monocytes/macrophages were fractionated by flow-cytometry and the total number of these cells was calculated. The total number of splenic cells was significantly increased by 1.18-fold after DADS administration. Among the lymphocyte subsets in the spleen, the number of B-lymphocytes significantly increased by 1.28-fold after DADS administration. The number of T-lymphocytes also showed a tendency to increase. However, the number of NK cells and monocytes/macrophages did not change after DADS administration. These results suggest that B-lymphocytes migrate from the circulation and translocate to the spleen in response to DADS administration.

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