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原著

メタボリックシンドロームの動物モデルであるSHR / NDmcr-cp（*cp* / *cp*）ラットの肝臓におけるチトクロームP4503A発現に対する食餌性魚油の影響

Vol.2、No.3、p.127-135

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概要 全文PDF [347K]

病態生理学的および栄養状態は、しばしば薬物代謝酵素の発現に影響を及ぼします。SHR / NDmcr-cp（*cp* / *cp*）ラット（SHR / NDcp）は、メタボリックシンドローム（MS）モデルとして非常に適しています。それにもかかわらず、SHR / NDcpの肝臓におけるシトクロムP450（CYP）の発現プロファイルについてはほとんど知られていません。したがって、CYP遺伝子の発現プロファイルと、SHR / NDcpの肝臓におけるこのプロファイルに対する魚油（FO）の影響を明らかにすることを試みました。低レベルのCYP3A2mRNAおよびCYP3A活性（テストステロン6β-ヒドロキシル化）は、対照（Wistar京都ラット（WKY）、自然発症高血圧ラット（SHR）、脳卒中を起こしやすいSHR、およびSHR /の痩せた同腹仔）と比較して、SHR / NDcpの特徴でした。 NDcp）。CYP3A2とは異なり、他のCYPアイソフォームの発現はSHR / NDcpでほとんど変化していませんでした。SHR / NDcpで観察されたCYPプロファイルの変化は、糖尿病および単純な脂肪肝の患者の変化と類似しています。高用量でFOを摂食する（18。食事中8%）肝臓でのCYP3A2遺伝子発現とCYP3A活性のアップレギュレーション。これらの増加の程度は、SHR / NDcpのWKYおよびリーン同腹子よりもSHR / NDcpの方が大きかった。この効果は、通常の用量（食事で5%）のFOでは観察されませんでした。これらの結果は、CYPプロファイルとの関連で、SHR / NDcpがMSの研究に適した動物モデルであることを示しており、MS患者における薬物の有効性または副作用を決定する上でFO摂取が重要であることを示唆しています。

ページトップ

原著

新薬の安全性評価における子宮発がんの懸念

Vol.2、No.3、p.117-126

黒田博之、山口貴史、木本敏子、小川修二、滋賀敦、奈良岡仁、高松和彦、大石雄二
リリース：2015年7月30日

概要 全文PDF [2M]

Acotiamide hydrochloride hydrate (acotiamide-HH) has been newly developed as an indication for functional dyspepsia, which is characterized by digestive symptoms such as postprandial fullness, abdominal bloating, or early satiation, and is now being prescribed in Japan. As part of a safety assessment, 2-year long-term carcinogenicity studies using rats and mice were conducted. In the mouse carcinogenicity study, no evidence of carcinogenicity was obtained, even in the high-dose-treated group (up to 2000 mg/kg/day). In the rat carcinogenicity study, acotiamide-HH was administered at 200, 600, and 2000 mg/kg/day. Detailed histopathological examination revealed that the incidence of endometrial adenocarcinoma significantly increased in the 600 mg/kg/day treated group. There was no trend of this incidence and no accompanying increase in pre-neoplastic lesions or related histological changes in the genital tissues, suggesting the absence of abnormalities in the sexual endocrine system. Results of genotoxicity and reproductive/developmental studies showed that acotiamide-HH is a non-genotoxic substance and did not affect sexual balance. Acotiamide-HH did not induce an estrogen-dominant hormonal imbalance that could

cause the incidence of uterine cancer and did not have initiation activity. Therefore, the proliferation of endometrial adenocarcinoma in this middle dose group in the rat carcinogenesis study was considered an accidental event of naturally occurring tumors. However, the incidence of endometrial adenocarcinoma in this group deviated from the background data collected in the same laboratory during the study period. Therefore, it is considered necessary to conduct another pre-clinical study in order to obtain data that would dispel any concerns of safety.

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Letter

Evaluation of laser irradiance on photodynamic therapy using talaporfin sodium-induced glioblastoma T98G cell death

Vol.2, No.3, p.111-116

Yuichi Miki , Jiro Akimoto , Aya Sato , Yasuyuki Fujiwara
Released: June 26, 2015

Abstract Full Text PDF[2M]

In photodynamic therapy (PDT) for glioma patients, apoptosis not necrosis is the desirable mode of cell death, as necrotic cell death induces late appearance of obstacles following PDT. We previously demonstrated that increase in both treatment dose of photosensitizer talaporfin sodium (NPe6) and laser fluence (laser energy density) changes the dominant cell death process from apoptosis to necrosis in glioblastoma T98G cells. Here, we investigated the effect of laser irradiance (laser power density), which is another important parameter of PDT, on PDT-induced cell death modalities in cultured T98G cells. When fluence was fixed at 10 J/cm^2, NPe6 dose-dependently reduced the cell viability, regardless of irradiance (11, 22, 33, and 44 mW/cm^2). Morphological observations and biochemical analysis (measurement of caspase-3 activity, staining of cell surface-exposed phosphatidylserine, and staining of propidium iodide) further confirmed that increase in dose of NPe6 changed the dominant cell death process from apoptosis to necrosis, regardless of irradiance. We also noted no influence of irradiance level on the leakage of lactate dehydrogenase from T98G cells following PDT treatment. Taken together, our present and previous findings suggest that dose of NPe6 and laser fluence but not laser irradiance are important parameters to consider in PDT using NPe6 in T98G cells.

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Letter

Positive and negative ions by air purifier have no effects on reproductive function or postnatal growth and development in rats

Vol.2, No.3, p.101-110

Dai Yamamoto , Yumi Wako , Shino Kumabe , Kiyoshi Wako , Yukari Sato , Mayumi Fujishiro , Yoshimasa Yasuda , Ikuo Matsuura , Yasuyuki Ohnishi
Released: June 23, 2015

Abstract Full Text PDF[181K]

Air purifiers, which release positive and negative ions generated by electric discharge, are widely used in a variety of places. In this study, male and female SD rats [Crl:CD(SD)] were exposed by whole-body inhalation (6 hr/day) to ionized air containing positive and negative ions for at least 10 weeks before mating and throughout the mating, gestation, and lactation periods over two generations, and the effects on the reproductive function of parental animals and development of offspring were assessed. The concentrations of the ionized air were set at 0 and 7,000,000 ions/cm3 (280- to 1,000-fold higher than normally used in humans) and each group consisted of 24 F0 rats/sex/group and 20 to 23 F1 rats/sex/group. The ionized air had no general toxicological effects on parental animals in the observation for clinical signs, body weight and food consumption measurement, or pathological examination. As for the effects on the reproductive function, there were no exposure-related changes in mating ability, fertility, pregnancy, parturition, or nursing behavior, nor were there any changes in the estrous cycle or sperm parameters in either generation, nor in the ovarian follicle counts (only F1 females). Moreover, there were no effects on litter size, viability,

growth, or development of F1 and F2 offspring, including sexual maturation. Therefore, it was suggested that the ionized air has no reproductive or developmental toxicity in rats.

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Original Article

Metabolism of trimethylselenonium ion in selenium accumulator, *Allium sativum* Vol.2, No.3, p.95-99

Yasumitsu Ogra , Yurie Ogihara , Yasumi Anan
Released: June 16, 2015

Abstract Full Text PDF[379K]

To understand selenium (Se) circulation in the biosphere, the metabolism of organic Se, in particular, Se metabolites, in animals and plants should be elucidated. In this study, garlic, *Allium sativum*, a well-known Se accumulator with high Se metabolic ability, was hydroponically cultivated and then exposed to trimethylselenonium ion (TMSe), a urinary metabolite. Thereafter, the Se concentration in several parts of garlic, such as roots, bulbs, and leaves, was determined. To reveal the metabolic pathway of TMSe, the Se species in *A. sativum*誘導結合プラズマ質量分析計（LC-ICP-MS）とハイフンでつながれたHPLCを使用したスペシエーションによって調査されました。Seは主に根に蓄積されていました。TMSeは各植物部分の抽出物で検出されました。しかし、培地から取り込まれたSeの量はニンニクに完全には回収されておらず、TMSeの一部が揮発性Seに代謝されたことを示唆しています。したがって、ニンニクに組み込まれたTMSeの大部分はそのまま蓄積され、残りは部分的に脱メチル化されて、ジメチル化Se化合物などの揮発性Se化合物を形成すると結論付けます。

ページトップ

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