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**Species differences between rats and dogs in LPS-stimulated Kupffer cells and monocytes.**

TAKAKO HAMANO[1], VINCENT TONG[1], MASAO HAYASHI[2], EIJI TANAKA[1], MAMORU MUTAI[1], [1]Toxicology Laboratory, Pharmaceuticals Research Division, Mitsubishi Pharma Corporation. Chiba 292-0812, Japan, [2]Depertment of Biology, Ochanomizu University, Tokyo, Japan

Kupffer cells (KCs) are the resident macrophages of the liver and represent the largest population of macrophages in mammalian body. Many reports have described KC-mediated cytotoxicity. We reported the species differences between rats and dogs in LPS-stimulated KCs cytotoxicity and cytokine (IL-1beta and IL-6) release. To assess the possibility of drug-induced KC-mediated cytotoxicity in humans, we compared monocytes (MCs) in the peripheral blood to KCs with regards to cytokine releases by LPS stimulation and LPS-bindings to cell membrane as well as investigating species differences in cytotoxicity. MCs showed the same responses to KCs; canine MCs have stronger cytotoxicity that rat MCs, and the amount of cytokine released from MCs following stimulation with LPS was greater in dogs that in rats. Canine KCs and MCs bind much LPS compared to rat KCs and MCs. These results suggest that drug effect to KCs could be alternatively estimated using MCs in blood.

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**Mechanisms of fatty liver induction by 3-methylcholanthrene (3-MC) in mice.**

HIROSHI KONDO, KAZUYUKI HIRATSUKA, FUMI ITOH, YOSHIHISA NAKANO, YUJI KAWAMURA, TOKI SAKAI, YASUHIRO SHINDO, Toxicology Laboratory, Meiji Seika Kaisha, Ltd., Yokohama 222-8567, Japan

Polyaromatichydrocarbons such as 3-MC are known to cause fatty liver and alteration of plasma lipid parameters in various animals. It is considered that an arylhydrocarbon receptor (AhR) is involved in causing these perturbations of lipid metabolism, however, detailed mechanism is still unknown. In this study, we investigated mechanism of 3-MC-induced fatty liver by comparing changes in the liver of C57BL/6N mice which express the AhR with a high affinity and those in the liver of DBA/2N mice which express the AhR with a low affinity. Six-week old male C57BL/6N and DBA/2N mice were given 3-MC once intraperitoneally at a dose of 100 mg/kg and euthanized 7 days after the administration for determination of liver weight and CYP1A activity, and liver histopathology. 3-MC caused an increase in liver weight, whitish and yellowish liver, and hypertrophy and vacuolation of hepatocytes in C57BL/6N mice 7 days after the treatment, which is suggestive of the formation of fatty liver. On the other hand, there were no such changes in DBA/2N mice. A marked increase in CYP1A activity was also observed in C57BL/6N mice compared to DBA/2N mice. These results indicate that an AhR is involved in the mechanism of 3-MC induced fatty liver. In order to evaluate how the failures in lipid transportation and beta-oxidation, and oxidative stress contribute to the fatty liver, we are now investigating time-course of VLDL secretion rate, lipid peroxidation and activity of beta-oxidation enzyme in the liver.