リノレン酸を負荷させた培養ラット肝細胞におけるアドリアマイシン誘発脂質過酸化

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Lipid Peroxidation induced by Adriamycin in Linoleic Acid-loaded cultured Hepatocytes

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ABSTRACT The addition of more than 10 μM of adriamycin to cultured rat hepatocytes which were loaded with α-linolenic acid (LNA-loaded hepatocytes) caused marked lipid peroxidation as measured by an accumulation of malondialdehyde(MDA) during a 9h incubation. After the addition of 50 μM of adriamycin to LNA-loaded hepatocytes, MDA accumulation significantly increased at 3h, followed by cellular GSH decrease and LDH leakage after 6h. The inhibition of the adriamycin-induced lipid peroxidation by the addition of DPPD or α-tocopherol, which are lipid radical scavengers, or deferoxamine, which is a Fe ion chelator, prevented both GSH decrease and LDH leakage, which indicated that lipid peroxidation caused the cellular damage to the LNA-loaded hepatocytes exposed to adriamycin. The effect of SKF 525-A, which is a specific cytochrome P450 inhibitor, on adriamycin-induced lipid peroxidation and on 7-ethoxycoumarin O-deethylase(ECD) activity was determined by a 6h incubation of LNA-loaded cells. The addition of SKF 525-A suppressed adriamycin-induced lipid peroxidation comparably with its ECD inhibitory activity. These results suggest that cytochrome P450(CYP) contributes to the one-electron bioreduction of adriamycin into its semiquinone radical in rat hepatocytes.

抄録 培養肝細胞にリノレン酸を取り込ませて、薬物の脂質過酸化に対する感受性を

増大させた脂肪肝細胞を用いて、アドリアマイシンによる脂質過酸化の性格付けを行った。アドリアマイシンは、脂肪肝細胞において鉄イオン依存性の脂質過酸化を誘起し、細胞内グルタチオンを減少させて細胞傷害を惹起した。又、SKF525-Aは7-ethoxycoumarin O-deethylase活性を阻害すると共に並行してアドリアマイシン誘発脂質過酸化を抑制した。従って、cytochrome P450がアドリアマイシンからセミキノンラジカルへの一電子還元に役割を果たしていることが示唆された。