四塩化炭素肝障害ラットにおける弱塩基性薬物の血漿蛋白結合

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Chem. Pharm. Bull. **39**(10) 2671–2673 (1991)

Increase in the Plasma Protein Binding of Weakly Basic Drugs in Carbon Tetrachloride-Intoxicated Rats

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ABSTRACT Plasma protein binding of weakly basic drugs such as propranolol and quinidine was determined in rats with carbon tetrachloride (CCl_4)-induced hepatic disease. Free fractions of Propranolol and quinidine in the plasma of rats at 24h after CCl_4-intoxication were decreased by 41 and 30%, respectively, compared to those of control rats. An addition of Tris (butoxyethyl) phosphate (TBEP), a specific displacer for basic drugs from α_1-acid glycoprotein (AGP), to the plasma increased the free fractions of the basic drugs, resuiting in no difference in the extent of the plasma free fraction of each drug between control and CCl_4-intoxcated rats.

Plasma concentration of AGP in CCl_4-intoxicated rats was elevated 2.7-fold of that in control rats at 24h after the CCl_4 intoxication and reached a peak of 4.8-fold elevation at 48h. A regression analysis revealed a high degree of positive correlation detween ratios of bound to free fraction of propranolol and plasma concentrations of AGP. These resuits suggets that the plasma protein binding of the ba—sic drugs was increased mainly due to the rise in the plasma AGP concentration in CCl_4-intoxicated rats.

抄録　プロプラノロールとキニジンの血漿遊離体の割合は，四塩化炭素投与24時間後のラット血漿においては，正常値に比べ，それぞれ，41と31%減少していた。弱塩基性薬物とα-酸性糖蛋白質（AGP）との結合を特異的に阻害するTBEPを血漿中に添加すると，薬物の血漿蛋白結合率は減少し，その結果，正常—四塩化炭素群間におけ

る薬物の血漿遊離体の割合にはプロプラノロール，キニジン共に，有意差が認められなくなった。次に，血漿AGP濃度を免疫拡散法で測定すると，肝障害ラットにおいては24時間後に正常値の2.7倍,48時間後に4.8倍にまで上昇していた。又，プロプラノロールの血漿蛋白結合率と血漿AGP濃度間には高い相関性が認められた。以上の結果から四塩化炭素肝障害ラットにおける弱塩基性薬物の血漿蛋白結合率の増加は血漿AGP濃度の上昇によるものと結論された。

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