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Narcotic drugs change the expression of cytochrome P450 2E1 and 2C6 and other activities of carcinogen-metabolizing enzymes in the liver of male mice.

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Source

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Abstract

Drug-metabolizing enzymes play a great role in the bioactivation and also detoxification of zenobiotics and carcinogens such as N-nitrosamines and polycyclic aromatic hydrocarbons (PAHs). Therefore, the present study was undertaken to investigate the effect of narcotic drugs such as cannabis (hashish) and diacetylmorphine (heroin) on the activity of N-nitrosodimethylamine N-demethylase I [NDMA-dI], arylhydrocarbon [benzo(a)pyerne] hydroxylase [AHH], cytochrome P450 (CYP), cytochrome b(5), NADPH-cytochrome c reductase, glutathione-S-transferase, and levels of glutathione and thiobarbituric acid-reactive substances (TBARS). In addition, the present study showed the influence of hashish and heroin after single (24 h) and repeated-dose treatments (4 consecutive days) on the expression of cytochrome P450 2E1 (CYP 2E1) and cytochrome P450 2C6 (CYP 2C6). The expression of CYP 2E1 was slightly induced after single-dose and markedly induced after repeated dose-treatments of mice with hashish (10 mg kg(-1) body weight). Contrarily, heroin markedly induced the expression of CYP 2C6 after single-dose and potentially reduced this expression after repeated-dose treatments. It is believed that N-nitrosamines are activated principally by CYP 2E1 and in support of this, the activity of NDMA-dI was found to be increased after single- and repeated-dose treatments of mice with hashish by 23 and 41%, respectively. In addition, single- and repeated-dose treatments of mice with hashish increased: (1) the total hepatic content of CYP by 112 and 206%, respectively; (2) AHH activity by 110 and 165%, respectively; (3) NADPH-cytochrome c reductase activity by 21 and 98%, respectively; (4) and glutathione level by 81 and 173%, respectively. Also, single-dose treatments of mice with heroin increased the total hepatic content of CYP, AHH, NADPH-cytochrome c reductase, and glutathione level by 126, 72, 39, 205%, respectively. However, repeated dose-treatments of mice with heroin did not change such activities except cytochrome c reductase activity increased by 20%. Interestingly, the level of free radicals, TBARS, was potentially decreased after single or repeated-dose treatments with either hashish or heroin. It is clear from this study that the effects of hashish are different from those of heroin

on the above mentioned enzymes particularly after repeated dose treatments. It is concluded that hashish induced the expression of CYP 2E1 and other carcinogen-metabolizing enzymes activities, and this induction could potentiate the deleterious effects of N-nitrosamines and aromatic hydrocarbons, e.g. benzo(a)pyrene, upon the liver and probably other organs. Such alterations may also change the therapeutic actions of other drugs, which are primarily metabolized by the P450 system, when administered to peoples using hashish or heroin.

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