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论著

心肌缺血再灌注损伤对大鼠肝细胞色素P450酶代谢的影响

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摘要 目的 探讨心肌缺血再灌注状态下，大鼠肝代谢功能和相关的氧化/抗氧化能力变化。方法 雄性SD大鼠随机分为5组，除假手术组外，制备在体心肌缺血再灌注模型，并于缺血40 min、再灌注15，60和180 min分别处死大鼠，检测血浆丙氨酸转氨酶(ALT)和天冬氨酸转氨酶(AST)活性，肝匀浆丙二醛(MDA)含量、超氧化物歧化酶(SOD)活性；以红霉素N-脱甲基酶、五氧基异噁唑O-脱乙基酶和苯胺羟化酶法为探针测定肝细胞色素P450(CYP)3A，CYP2B1和CYP2E1催化功能；RT-PCR法检测肝Ⅰ相药物代谢酶CYP3A1，CYP2B1/2，CYP2E1，以及Ⅱ相解毒酶NAD(P)H醌氧化还原酶(NQO1)及其上游因子NF-E2相关因子(Nrf2)mRNA水平。结果 再灌注60 min，肝匀浆MDA含量升高(P<0.05)，SOD活力下降(P<0.01)；再灌注180 min时，血浆ALT和AST活性升高(P<0.05)。Nrf2基因于再灌注60 min时显著激活(P<0.05)，下游因子NQO1 mRNA于再灌注180 min时明显上调(P<0.05)。CYP3A催化功能和mRNA水平分别于再灌注60和180 min开始明显降低(P<0.05)；CYP2B1/2 mRNA和催化功能水平分别于再灌注15和180 min开始明显降低(P<0.05)；CYP2E1催化功能无明显改变。结论 大鼠心肌缺血再灌注可引起肝组织氧化应激及并导致功能损伤。在再灌注早期，具有抗氧化功能的NQO1在转录水平显著上调，其机制可能与上游因子Nrf2被激活相关；CYP3A和CYP2B催化功能在转录和(或)转录后水平明显下调。

关键词 心肌缺血 再灌注损伤 细胞色素P450 CYP3A 细胞色素P450 CYP2B

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Effects of myocardial ischemia/reperfusion injury on metabolism of liver cytochrome P450 enzymes in rats

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Abstract

OBJECTIVE To investigate the effects of myocardial ischemia/reperfusion injury (MIRI) on the metabolizing ability and related change in oxidative/antioxidative capacity in rats. **METHODS** Male SD rats were divided into 5 groups, and received the operation to establish model of the myocardial ischemia except the sham operation control group. After myocardial ischemia for 40 min, rats were respectively sacrificed at 15, 60 and 180 min of reperfusion. Plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities as well as hepatic malondialdehyde(MDA) content and superoxide dismutase (SOD) activity were detected. The catalytic activities of hepatic cytochrome P450 (CYP)3A, CYP2B1 and CYP2E1 were measured by erythromycin N-demethylase, pentoxyresorufin O-deethylase and aniline hydroxylase, respectively. CYP3A1, CYP2B1/2, CYP2E1, phase Ⅱ detoxicating enzyme NAD(P)H quinone oxidoreductase 1 (NQO1) and its upstream factor NF-E2-related factor (Nrf2) mRNA were determined by RT-PCR. **RESULTS** At reperfusion for 60 min, hepatic MDA content began to elevate (P<0.05); meanwhile, SOD activity decreased (P<0.01). Plasma ALT and AST activities increased at 180 min of reperfusion (P<0.05). Nrf2 mRNA level was elevated at 60 min of reperfusion (P<0.05), and its downstream factors NQO1 gene expression also increased after 180 min of reperfusion (P<0.05). CYP3A activity levels and mRNA obviously decreased, respectively, at 60 min and 180 min of reperfusion (P<0.05). The levels of CYP2B mRNA and activity decreased, too, respectively, at 15 min and 180 min of reperfusion (P<0.05). No change in the catalytic activity of CYP2E1 was observed at any time points of reperfusion. **CONCLUSION** MIRI results in the hepatic

oxidative stress which is followed by the reduction of liver function. At early stage of reperfusion,